Published in final edited form as:

Neurology. 2008 May 6; 70(19 Pt 2): 1809–1817. doi:10.1212/01.wnl.0000303814.13509.db.

A randomized placebo-controlled trial of Ginkgo biloba for the prevention of cognitive decline

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Abstract

Objective—To assess the feasibility, safety, and efficacy of Ginkgo biloba extract (GBE) on delaying the progression to cognitive impairment in normal elderly aged 85 and older.

Methods—Randomized, placebo-controlled, double-blind, 42-month pilot study with 118 cognitively intact subjects randomized to standardized GBE or placebo. Kaplan-Meier estimation, Cox proportional hazard, and random-effects models were used to compare the risk of progression from Clinical Dementia Rating (CDR) = 0 to CDR = 0.5 and decline in episodic memory function between GBE and placebo groups.

Results—In the intention-to-treat analysis, there was no reduced risk of progression to CDR = 0.5 (log-rank test, $p = 0.06$) among the GBE group. There was no less of a decline in memory function among the GBE group ($p = 0.05$). In the secondary analysis, where we controlled the medication adherence level, the GBE group had a lower risk of progression from CDR = 0 to CDR = 0.5 (HR = 0.33, $p = 0.02$), and a smaller decline in memory scores ($p = 0.04$). There were more ischemic strokes and TIAs in the GBE group ($p = 0.01$).

Conclusions—In unadjusted analyses, Ginkgo biloba extract (GBE) neither altered the risk of progression from normal to Clinical Dementia Rating (CDR) = 0.5, nor protected against a decline in memory function. Secondary analysis taking into account medication adherence showed a protective effect of GBE on the progression to CDR = 0.5 and memory decline. Results of larger prevention trials taking into account medication adherence may clarify the effectiveness of GBE. More stroke and TIA cases observed among the GBE group requires further study to confirm.

One of the most pressing public health problems facing society in the coming decades is the rapidly growing number of aging individuals who, because of their age alone, are highly susceptible to dementia.¹ Because of this major increase in those affected with dementia, the potential of delaying or preventing cognitive decline before onset of symptoms (primary prevention) is thus of great importance. Very few studies of primary prevention of dementia have been completed. In part, this is related to the challenges of conducting such studies which include selection of non-toxic agents to be administered over long follow-up periods in relatively large subject cohorts. Given these challenges, one approach toward developing

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Disclosure: The authors report no conflicts of interest.

optimized dementia prevention studies is to focus on high-risk (for developing dementia) populations using readily available agents.

In this article we describe the results of a randomized placebo-controlled primary prevention trial of standardized Ginkgo biloba extract (GBE) designed for the purpose of demonstrating that 1) a primary prevention trial in the high risk for dementia, oldest old (age ≥ 85) is feasible; 2) GBE is safe in the oldest old; and 3) there is a trend for GBE to delay the onset of progression to cognitive impairment. The study was designed within a constrained budget, conceived of as a feasibility study and as a means to estimate future study sample sizes. The oldest old age group was chosen as a focus since over 50% of those with dementia in developed countries currently are octogenarians or older, and the rate of transition to dementia in this age group is approximately 8 to 15% per year.² Thus this group is highly relevant from a public health standpoint as well as for addressing the practical consideration of being able to observe a reasonable number of transition-to-dementia events over a typical observation period of several years. GBE was chosen as a prevention agent because 1) it is already widely used even among the oldest old,³ 2) it has been shown in preclinical studies to have plausible biologic efficacy acting as an antioxidant and on other important brain aging mechanisms,⁴ 3) prior dementia clinical trials have suggested efficacy in manifest Alzheimer disease (AD),^{5,6} 4) there is anticipated to be a favorable safety profile, and 5) the use of GBE, if effective and safe, could be widely adopted since it is already available and relatively inexpensive to administer and follow as a treatment.

METHODS

The Oregon Center for Complementary and Alternative Medicine in Neurological Disorders and NIA-Layton Aging and AD Center conducted a 42-month, randomized, double blind, placebo controlled pilot trial of standardized GBE 240 mg daily (Thorne Research, Inc., Sandpoint, ID) (80 mg, 3 times a day) to determine the effect of GBE on cognitive decline among oldest old subjects. The study sample was targeted to enroll 135 subjects. GBE samples were independently verified (Alpha Labs, Petaluma, CA) to have at least 6% terpene lactones and 24% flavone glycosides. All participants also received a standard multivitamin containing 40 IU of vitamin E to decrease the temptation to intermittently experiment with supplements during the course of the trial. Detailed inclusion and exclusion criteria for this study are given in table 1. Briefly, entry criteria were 1) age 85 or older, 2) informant available, 3) no subjective memory complaint, 4) normal memory function defined by an education-adjusted score on the Logical Memory Subscale of the Wechsler Memory Scale-Revised (WMS-R),⁷ 5) Mini-Mental State Examination Score (MMSE)⁸ > 23 , 6) Clinical Dementia Rating (CDR)^{9,10} = 0, and 7) free from depressive symptoms defined by Center for Epidemiologic Studies Depression Scale (CES-D-10)¹¹ < 4 .

Participants

The study protocol and informed consent process met requirements set by the Institutional Review Board of Oregon Health & Science University (OHSU); all subjects signed written informed consent (IRB #687). Participants were recruited primarily through mass mailings to age-eligible individuals in the greater Portland area. Mailing lists were obtained from the Oregon Department of Motor Vehicles and Oregon Voter Registration Office. The combined lists included over 30,000 records. From August 2000 to September 2001, informational letters were sent randomly to 10,700 individuals. Individuals were asked to return a contact sheet with a phone number in a self-addressed, stamped envelope. In addition, participants were recruited using existing volunteer resources at the Layton Aging and AD Research Center at OHSU. We received intention to participate into the study from 636 subjects.

Timeline of assessments

All subjects were initially screened by telephone to prescreen for obvious medical exclusions (table 1). Cognitive status was further screened by telephone using the Blessed Orientation Memory Concentration Test.^{12,13} Individuals were required to have error scores below 12 to be further screened in person. This cutoff is higher than the commonly used cutoff score of 9 to take into account hearing deficits among prospective participants. In-home screening interviews were completed by trained research assistants and included informed consent, cognitive screening assessments, medical history review, and taking a blood sample for screening tests (for common causes of dementia, including a metabolic panel and CBC). An MRI scan of the brain was also completed. Subjects' primary care medical records were obtained (with subjects' consent for medical information release) and reviewed for inclusion and exclusion criteria. Subjects meeting all criteria were then randomly assigned to treatment group with either GBE or placebo using a computer-generated modified randomized minimization algorithm.¹⁴ Factors we balanced are age, sex, years of education, and MMSE scores. Assignment was made by a statistician (not evaluating the data) and all other study personnel were blind to the assignment.

The participants underwent annual in-person interviews with 6-month follow-up visits to assess health status changes, MMSE, depressive symptoms, activities of daily living, medication review, pill count, and health history review (new hospitalizations, new diagnoses, or adverse events). Annual visits included extensive cognitive testing of major cognitive domains and clinical examinations. Apolipoprotein E genotyping was completed at baseline. This study period includes data until the end of the trial for up to 42 months (3.5 years) of follow-up (baseline and seven follow-up time points).

Outcome

Three outcomes were examined: 1) Mild cognitive decline defined as progression from CDR = 0 to CDR = 0.5. CDR was rated every year by a neurologist and every 6 months by trained study research assistants, based on interviews with the participant and collateral informant. For the current analyses, the outcome of interest is progression from CDR = 0 to CDR = 0.5, i.e., the time at which the subject received CDR = 0.5 for the first time; 2) Decline in memory function over time measured by Consortium to Establish a Registry for AD 10-word Word List Delayed Recall test¹⁵; and 3) Adverse events.

Variables examined

The characteristics examined for placebo and GBE groups include the following variables at baseline: basic demographic variables including age, sex, years of education, and living arrangement (living alone vs living with someone), and MMSE, CES-D-10 for depressive symptoms, apolipoprotein e4 (at least one e4 allele vs no e4), a modified Cumulative Illness Rating Scale (mCIRS)¹⁶ as an indicator of disease burden, the number of prescription medications taken (Rx Meds), and a medication adherence level. At each visit, interviewers used a counting board to get an exact count of remaining pills, then used an Excel-based program to calculate the % compliance based on the number of remaining pills, number presumably taken, number prescribed, and the number of days since the last pill count. Since the medication adherence could change due to decline in cognitive function, we used the adherence level during the first 6 months (i.e., a baseline medication adherence level). The medication adherence level was examined as a continuous variable and also as a dummy variable using a definition of medication adherers being those who took medication at or above 80%, but less than 110% of prescribed pills based on the pill count. By study design, age, sex, years of education, and MMSE are expected to have the same distribution between GBE and placebo groups. In the secondary analysis, we first controlled medication adherence level during the first 6 months to control the actual amount of GBE consumed and possible factors

associated with medication adherence. Next we also controlled other variables described above in statistical models. Adverse events were defined as those which required hospitalization or emergency department visit based on the reports from the participants or informants at the follow-up (every 6 months) and also assessed by medical charts annually.

Statistical methods

The baseline characteristics associated with GBE vs placebo groups and the level of medication adherence were assessed using χ^2 tests for categorical variables, and t test and Mann-Whitney nonparametric test, the latter for non-normally distributed continuous variables.

Primary analysis—We examined Kaplan-Meier survival curves (outcome event: progression to CDR = 0.5) and person years conversion rate of progression from CDR = 0 to CDR = 0.5 among placebo and GBE groups. The hazard ratio of progression from normal to CDR = 0.5 between GBE and placebo groups was obtained through a Cox Proportional Hazard model. The effect of GBE on decline in memory function was examined using the random-effects model¹⁷ with the following covariates: a prevention group (GBE vs placebo), time (from baseline), and the interaction of time and a prevention group. The random-effects model allows for within-person variability in initial cognitive score and in slope of change. The coefficient of a prevention group indicates differences in baseline delayed recall test score between GBE and placebo. The coefficient of time indicates changes in test scores by one unit increase in time (every 6 months). The coefficient of the interaction term of time and the prevention group indicates whether the GBE group experienced less (or more) decline, compared with the placebo group, which is our main interest. The overall and event specific proportions of subjects who reported adverse events were compared between the GBE and placebo groups using Fisher exact test.

Secondary analysis—We first controlled for medication adherence level during the first 6 months in the Cox Proportional Hazard Model and in the random-effects model. Next we also controlled for other covariates described above including age, sex, years of education, and living arrangement (living alone vs living with someone), and MMSE, CES-D-10, apolipoprotein e4 (at least one e4 allele vs no e4), mCIRS, and Rx Meds. The proportionality assumptions were examined through visual inspection of survival curves ($-\ln[-\ln S(t)]$) as well as statistical assessments.¹⁸

RESULTS

Primary analysis

Figure 1 details the flow of the study participants. Among 636 subjects who responded to our initial invitation to participate in our study, 412 (64.8%) were excluded during the telephone screening, and 90 (14.2%) were excluded at the initial home screening. A total of 190 subjects (29.8%) declined study participation after being contacted by interviewers. Among the remaining 134 subjects randomized to placebo or GBE group, 9 subjects developed exclusionary medical conditions before any follow-up visits and were excluded from the study, and 3 subjects refused to participate further without any specific reasons. An additional 4 subjects were excluded from the analyses because they were missing at least one of the variables of interest. Data from the remaining 118 participants were used in this study. The 16 subjects (134 - 118) who were excluded from the current analysis were not significantly different in any demographic variables (age, sex, and years of education) from those included in the analysis. Among the 118 subjects with CDR = 0 at baseline, 60 subjects (50.8%) were in the GBE group and 58 subjects (49.2%) were in the placebo group. Twenty-one subjects (17.8%) progressed to CDR = 0.5 during the 42 months of follow-up: 14 cases among placebo group and 7 cases among GBE group. Eighteen of these 21 cases had at least two consecutive CDRs

of 0.5; 2 cases died after the first observation of CDR = 0.5 without further follow-up, and one reached the study termination (42 months) after two nonconsecutive observations of CDR = 0.5. Subsequent progression to CDR $\geq$ 1.0 during the follow-up was observed for 4 out of 21 cases: 3 among placebo group and 1 among GBE group. Dropout was not different between the GBE and placebo groups over the 42-month period; during the 42-month period, we observed 16 deaths (26.6%) among the GBE group and 13 deaths (21.6%) among the placebo group ($p = 0.57$). Nonmortality dropout (dropout not due to death) during the 42-month period was low and not different between the GBE (5 subjects, 8.3%) and the placebo (5 subjects, 8.6%) groups.

The mean duration (SD) of follow-up for total sample was 3.15 (0.88) years: 3.00 (0.98) years for placebo group and 3.29 (0.77) years for GBE group. The conversion rates from CDR = 0 to CDR = 0.5 were 80.4 per 1,000 person-years among placebo group and 35.4 per 1,000 person-years for GBE group. Figure 2 shows the Kaplan-Meier survival curves with event being the progression to CDR = 0.5. The survival curves showed that the GBE group has a lower likelihood of progression from normal to CDR = 0.5; log-rank test showed χ^2 value of 3.37 (p value = 0.06).

Table 2 shows the characteristics associated with GBE and placebo groups. The two groups were not significantly different on any of the variables examined. Overall 68.6% of participants met our definition of medication adherers: 65.0% among GBE group and 72.4% among placebo group. Five subjects took more than the prescribed number of pills: 2 subjects among the GBE (102% and 140%) and 3 subjects (104%, 117%, and 118%) among the placebo group.

The results of Cox proportional hazard regression model and random-effects model with a prevention group as a covariate are shown under Model 1 in tables 3 and 4. The hazard ratio of GBE (placebo as a reference group) on progression to CDR = 0.5 was 0.43 (95% CI: 0.17 to 1.08, $p = 0.066$). The effect did not reach the predefined statistical significance. The coefficient of the interaction term of a prevention group and time in random-effects model was 0.111 ($p = 0.055$); GBE group showed a tendency of less decline in memory function over time, but it was slightly greater than the prespecified 0.05 level of statistical significance.

There was no overall difference in adverse events (table 5) reported by subjects in the GBE group, compared to subjects in the placebo group (difference in proportions, $p = 0.44$). However, the GBE group had more stroke or TIA incidences (7 reports, 11.7%) compared with the placebo group (0 report) ($p = 0.01$, uncorrected for multiple comparisons). All strokes were nonhemorrhagic infarcts except one case; the subject with hemorrhagic infarct continues to participate in the study after the event. There were no deaths due to stroke. Four out of seven participants with stroke incidence continued to participate in the study. There was no difference in the incidence of hemorrhagic events such as gastrointestinal ulcer, epistaxis, or ecchymoses. Mortality was not different between the groups (five subjects among each group).

Secondary analysis

The results of Cox proportional hazard models with additional covariates are shown under Models 2 and 3 in table 3. When we controlled for baseline medication adherence level, GBE showed a protective effect (HR = 0.33, 95% CI 0.12 to 0.89) on progression from CDR = 0 and CDR = 0.5. The results did not change after we controlled for other covariates at baseline (HR = 0.32, 95% CI 0.11 to 0.93). Among control variables, only depressive symptoms predicted progression; one unit increase in depressive symptoms was associated with a 79% increase in the risk of progression from CDR = 0 to CDR = 0.5 (HR = 1.79, 95% CI 1.12 to 2.89).

Models 2 and 3 in table 4 show the results of random-effects models with additional covariates. Once we control medication adherence level (Model 2), GBE showed a protective effect against cognitive decline; the coefficient of the interaction term of time and a prevention group was 0.11 ($p = 0.04$), indicating that the GBE group had less decline compared to the placebo group. However, once we controlled other covariates at baseline, GBE did not show a protective effect ($p = 0.06$). Among covariates, we found higher levels of medication adherence, being a woman, higher educational attainment, and higher MMSE score at baseline were associated with higher baseline Delayed Recall test scores.

As a post hoc analysis, we examined whether lower medication adherence is associated with higher depressive symptoms. The logistic regression model with the outcome being medication nonadherence (nonadherence level based on pill counts $\leq 80\%$, or $\geq 110\%$) showed no association between these two variables ($p = 0.48$).

DISCUSSION

In this study of GBE as a primary prevention for cognitive decline, we examined the feasibility of randomizing and following a cohort of seniors at high risk for cognitive decline (the oldest old) in a standard clinical trial for up to 42-months using a non-prescription medication. Importantly, subjects did not exhibit unusual levels of dropout with only 29 deaths (24.5%) and 10 non-mortality related dropouts (8.5%) during the 42-month study. This may reflect the relatively healthy nature of this volunteer sample of the oldest old. However, they did have common stable medical conditions such as heart disease and hypertension. Although not formally recorded as part of the study, we generally observed that many subjects were highly motivated and pleased to contribute to science and to “feel useful” at an advanced age.

Observed excess bleeding-related complications associated with Ginkgo have been reported.¹⁹ There were no observed excess bleeding-related complications in this study, but we did observe more strokes (6 cases) and TIA (1 case) in the GBE group. The stroke cases except one were not hemorrhagic, were generally not severe (only two subjects required institutional long-term care), and there were no deaths. The increased stroke risk will require further close scrutiny in other GBE prevention trials.

The absence of a protective effect of GBE against progression to CDR = 0.5 in this pilot study is potentially related to the limited statistical power of this relatively small number of participants and short duration of follow-up. However, we obtained a consistent, independent signal of a possible protective effect in that the delayed recall scores (which were independent of the CDR assessment) showed the same trend. Based on the data from this trial we estimate that we would need at least 300 subjects followed for the same period of time with similar proportions of death, dropout, and cognitive decline as in the current study to obtain 80% power to detect the significant effect of GBE, given a true hazard ratio of 0.5 (i.e., GBE group has 50% reduction in risk of progression to CDR = 0.5). Given a true hazard ratio of 0.8 (i.e., GBE group has 20% reduction in the risk of progression to CDR = 0.5), we would need over 2,800 subjects to attain 80% power. Obtaining this sample size may require a large sampling frame from which to draw the sample and could limit larger study feasibility. Our method was originally focused on a single metropolitan population, mail-based sampling approach using existing driving and voter registration lists containing over 10,000 oldest old (over 30,000 people over the age of 84 live in this area). Because of budgetary constraints, no special advertising or recruitment methods were used, which would likely increase the number of subjects who would participate. In general, studies of this size are conducted as multicenter efforts. Ongoing larger GBE trials^{20,21} are powered using much larger samples on the assumption that the transition rates to cognitive impairment are low (especially in younger elderly) and the efficacy of GBE may be modest. Our data suggest that these other studies

should be able to definitively establish a brain protective effect of GBE assuming that such variables as the dosing and the nature of the population samples enrolled (i.e., these other studies have a younger elderly population under treatment) are not major determinants of efficacy.

The results of the primary outcome of interest (conversion to CDR 0.5) did not appear to be affected by a number of variables that have been suggested to influence the susceptibility to dementia including sex, education, chronic medical illnesses, and apolipoprotein E genotype. In the covariate analyses only depression score and treatment group were significant. The mean depression scores were very low with no subject qualifying for clinically significant depression and thus the practical significance of this observation is uncertain.

Given the finding of an effect on efficacy based on medication adherence, we were particularly interested in conducting careful exploratory studies based on statistical models with the medication adherence level as a control variable. This was because medication management ability is highly associated with cognitive functioning among the elderly.²²⁻²⁶ This poses a unique problem for dementia prevention studies because 1) participants are usually non-institutionalized elderly volunteers and their medication adherence cannot be fully controlled, 2) those with subclinical dementia might experience a decline in medication adherence prior to the clinical manifestation of the disease, and 3) depression which was shown to be a premorbid condition or a risk factor of dementia²⁷ could also affect medication adherence.²⁸⁻³⁰ That is, lower adherence would decrease the benefit of GBE, but a lower adherence level is associated with declining cognitive abilities. Thus, it is difficult to evaluate the efficacy of the active agent. Additionally, the potentially very high correlation between study outcome and average medication adherence level during the follow-up, for example, would mask the effect of preventive agents on the outcome. How to best examine efficacy of an active agent in the face of potential development of memory decline that impairs treatment adherence in dementia prevention studies is an important challenge. If the duration of surveillance prior to developing dementia was sufficiently long, one could take the average medication adherence levels at least several years prior to the dementia incidence, assuming that subjects were free from subclinical stage disease during these years. It will be important in future prevention trials to incorporate such considerations into the design and analysis strategies of these studies.

Under all circumstances methods to facilitate and increase adherence in dementia prevention trials will be critical. One simple goal is, where possible, to use once a day dosing. The optimal dosing regimen for GBE is not known.⁶ In our study, we used three times a day dosing and found the overall mean medication adherence level defined as the average percentage of pills taken during the first 6 months was 84%. Over 68% of study participants met our criteria for being adherent (80% or higher and 110% or lower based on pill counts) during the first 6 months regardless of whether they were taking active drug or placebo. This is very similar to three times a day dosing adherence rates found in a systematic review of 57 studies of medication adherence in younger populations using electronic monitors.³¹ Although age has not been a significant correlate of adherence in other analyses,³² our study extends the age range well beyond that in most of the earlier studies and further demonstrates the feasibility of conducting trials in the oldest old.

The suggestive results of a protective effect of GBE found in our study needs to be confirmed by ongoing larger prevention studies such as the Ginkgo Evaluation of Memory study in the US²¹ and the European GuidAge study.²⁰ To our knowledge, our study is the first to report the results of a dementia prevention RCT among oldest old subjects. The results suggest that this population should not be excluded because of preconceived notions of frailty, poor adherence, or confounding medical problems, but to the contrary, may be a highly informative group to study especially in initial early phase II prevention designs because of their higher

susceptibility to dementia and growing relevance to the demographics of those most affected with dementia. More stroke and TIA cases were observed among the GBE group, which requires further study in other GBE prevention trials.

ACKNOWLEDGMENT

The authors thank Dr. Mary Ganguli at the University of Pittsburgh and Dr. Peter Lachenbruch at the Oregon State University for comments. Ginkgo biloba extract and placebo capsules were provided by Thorne Research, Inc. (Sandpoint, ID).

Supported by P50 AT00066 from the National Center for Complementary and Alternative Medicine, P30 AG08017, and K01 AG023014 from National Institute on Aging.

GLOSSARY

AD, Alzheimer disease; CDR, Clinical Dementia Rating; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CES-D, Center for Epidemiologic Studies Depression Scale; GBE, Ginkgo biloba extract; mCIRS, modified Cumulative Illness Rating Scale; MMSE, Mini-Mental State Examination Score; OHSU, Oregon Health & Science University; WMS-R, Wechsler Memory Scale-Revised.

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Figure 1.
Flow diagram

Figure 2.
Kaplan-Meier survival curves for Ginkgo biloba extract and placebo groups

Table 1
Detailed inclusion and exclusion criteria

Inclusion criteria
1. Age > 84 years
2. No subjective complaint of memory impairment compared to others of their own age
3. Has not sought assessment for memory or cognitive dysfunction
4. Normal memory function defined by an education-adjusted score on the Logical Memory Subscale of the Wechsler Memory Scale-Revised:
a. >8 for 16 or more years of education
b. > or = 4 for 8-15 years of education
c. >2 for 0 -7 years of education
5. Mini-Mental State Examination score >23
6. Blessed Orientation Memory Concentration Test (Telephone Screen) <12
7. Functionally independent (ADL= 0)
8. Clinical Dementia Rating = 0
9. Absence of significant depressive symptoms: CES-D-10 score < 4
10. Sufficient vision and hearing to complete all testing
11. Sufficient English language skills to complete all testing
12. General health status that will not interfere with ability to complete longitudinal study (conditions that will likely lead to this problem are listed below in the study exclusions list)
13. Informant available with frequent (at least 1 hour per day 3 days a week) contact with subject to verify functional status.
Exclusion criteria
1. Diseases associated with dementia such as Alzheimer disease, ischemic vascular dementia, normal pressure hydrocephalus, or Parkinson disease
2. Significant disease of the CNS such as brain tumor, seizure disorder, subdural hematoma, cranial arteritis
3. Current (within the last 2 years) alcohol or substance abuse according to DSM-IV criteria
4. Major depression, schizophrenia, or other major psychiatric disorder defined by DSM-IV criteria
5. Abnormal laboratory values indicating B12 deficiency, thyroid disease, or urinary tract infection (documented chronic bacterial colonization is acceptable)
6. Unstable or significantly symptomatic cardiovascular disease such as coronary artery disease with frequent angina, or congestive heart failure with shortness of breath at rest
7. Insulin dependent diabetes mellitus
8. Active systemic cancer within 5 years of study entry (Gleason Grade <3 prostate cancer, and non-metastatic skin cancers are acceptable)
9. Illness that requires >1 visit per month to a clinician
10. Progressive vision loss (age-related macular degeneration already beginning to significantly degrade vision)
11. Need for oxygen supplementation for adequate function
12. Medications:
a. Frequent use of high doses of analgesics
b. Sedative medications except for those used occasionally for sleep (use limited to no more than twice per week)
c. Subjects taking CNS-active medications that have not been on stable doses for at least 2 months including cimetidine, beta-blockers, and selective serotonin reuptake inhibitors
d. Subjects taking neuroleptics, antiparkinsonian agents, systemic corticosteroids, and narcotic analgesics; in the case where these were used for a self-limited time they must have been discontinued for a period of five half-lives prior to baseline
e. Subjects will not be excluded if they are taking other over-the-counter supplements, but the dose must not be changed during the course of the trial unless medically indicated; the presence and dose of these agents will be recorded
f. Subjects taking cholinesterase inhibitors
g. Use of investigational drugs within five half-lives prior to baseline
ADL = activities of daily living; CES-D = Center for Epidemiologic Studies Depression Scale; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders.

Table 2

Characteristics of GBE and placebo groups

Variables	GBE, n = 60	Placebo, n = 58	Difference <i>p</i> value
Age at baseline, y, mean (SD) (range)	87.50 (2.14) (85-94.1)	87.43 (2.22) (85-94.1)	0.62 [*]
Women, %	58.33	63.16	0.54 [†]
Years of education, mean (SD)	13.88 (2.93)	13.65 (2.42)	0.69 [‡]
Living alone, %	56.67	61.40	0.55 [†]
Having one or more apoE4 alleles, %	16.67	21.05	0.57 [†]
10-Items Center for Epidemiological Studies Depression Scale score, mean (SD)	0.71 (0.92)	0.67 (0.86)	0.87 [*]
Number of prescription medications, mean (SD)	2.88 (1.82)	2.35 (1.73)	0.11 [*]
Modified Cumulative Illness Rating	22.18 (3.40)	21.43 (3.11)	0.21 [‡]
Mini-Mental State Examination score, mean (SD)	28.47 (1.40)	28.18 (1.42)	0.24 [*]
CERAD 10-word Word List Delayed Recall test (SD)	5.53 (0.21)	5.76 (0.28)	0.31 [‡]
Drug adherence during the first 6 months based on pill counts, mean / median % (range)	82.5/91.0 (0-140.0)	85.4/92.1 (31.0-118.0)	0.57 [*]
% Meeting the targeted adherence level (80% ≤ adherence level ≤ 110% based on pill counts) during the first 6 months	65.0	72.4	0.38 [†]

GBE = Ginkgo biloba extract; CERAD = Consortium to Establish a Registry for Alzheimer's Disease.

^{*} Mann-Whitney test.[†] Pearson χ^2 test.[‡] *t* Test.

Table 3
Effect of Ginkgo on the risk of progression to CDR = 0.5: Results of Cox proportional hazard model (n = 118)

Variables	Model 1		Model 2		Model 3	
	HR	95% CI	HR	95% CI	HR	95% CI
Ginkgo (reference: placebo)	0.43	(0.17, 1.08)	0.33*	(0.12, 0.89)	0.32*	(0.11, 0.93)
Adherence level during the first 6 months			0.98	(0.96, 1.00)	0.98	(0.97, 1.00)
Age					1.10	(0.90, 1.35)
Female					0.82	(0.31, 2.14)
Years of education					0.88	(0.71, 1.09)
10-Items Center for Epidemiological Studies Depression Scale score					1.79*	(1.12, 2.87)
Having one or more ApoE4 alleles					2.35	(0.74, 7.40)
Modified Cumulative Illness Rating Scale					1.02	(0.85, 1.21)
Numbers of prescription medication taken					0.83	(0.63, 1.11)
Mini-Mental State Examination score					0.81	(0.58, 1.14)

CDR = Clinical Dementia Rating.

* Significant at $p < 0.05$.

Table 4
Result of random-effects model on CERAD word list delayed recall score over time

Variables	Model 1		Model 2		Model 3	
	Coefficient (SE)	p Value	Coefficient (SE)	p Value	Coefficient (SE)	p Value
Time	-0.122* (0.045)	0.008	-0.163 (0.114)	0.156	-0.126 (0.119)	0.291
GBE	-0.384 (0.303)	0.206	-0.299 (0.292)	0.306	-0.376 (0.259)	0.147
Interaction of time & GBE (Time × GBE)	0.111 (0.057)	0.055	0.115* (0.057)	0.047	0.103 (0.056)	0.069
Adherence level during the first 6 months			0.017* (0.005)	0.002	0.012* (0.005)	0.016
Time × adherence level during the first 6 months			0.000 (0.001)	0.693	0.000 (0.000)	0.980
Age					-0.085 (0.053)	0.111
Female					0.592* (0.249)	0.018
Years of education					0.082* (0.039)	0.035
10-Items Center for Epidemiological Studies Depression Scale score					-0.150 (0.118)	0.203
Having one or more ApoE4 allele					-0.363 (0.342)	0.288
Modified Cumulative Illness Rating Scale					0.080 (0.041)	0.051
Numbers of prescription medication taken					-0.074 (0.069)	0.288
Mini Mental State Examination score					0.042* (0.083)	<0.001

GBE = Ginkgo biloba extract; CERAD = Consortium to Establish a Registry for Alzheimer's Disease.

* Significant at $p < 0.05$.

Table 5

Adverse events

Events, n (%)	GBE, n = 60	Placebo, n = 58	<i>p</i> Value (Fisher exact test)
Cardiac	9 (15.0)	10 (17.2)	0.80
Hypertension	1 (1.7)	0	1.00
Hematologic	1 (1.7)	2 (3.5)	0.61
Respiratory	4 (6.7)	3 (5.2)	1.00
Eyes, ears, nose, and throat	2 (3.3)	1 (1.7)	1.00
Gastrointestinal	7 (11.7)	3 (5.2)	0.32
Renal	1 (1.7)	1 (1.7)	1.00
Genitourinary	4 (6.7)	4 (6.9)	1.00
Musculoskeletal (includes fractures)	3 (5.0)	7 (12.1)	0.20
Falls	4 (6.7)	7 (12.1)	0.35
Stroke/TIA	7 (11.7)	0	0.01 [*]
Endocrine-metabolic	0	2 (3.5)	0.23
Malignancy	1 (1.7)	4 (6.7)	0.20
Others (dizziness, fatigue, vertigo, blurred vision)	2 (3.3)	2 (5.2)	1.00
Total no. of events reported	46	46	0.82
Total no. of subjects with adverse events[†]	29 (48.3)	31 (53.5)	0.58

GBE = Ginkgo biloba extract.

^{*} Significant at $p < 0.05$.[†] Due to multiple events reported per subject, the total number of subjects with adverse events is smaller than the total number of events reported.