The Efficacy of Ginkgo biloba on Cognitive Function in Alzheimer Disease

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Objective: To determine the effect of treatment with Ginkgo biloba extract on objective measures of cognitive function in patients with Alzheimer disease (AD) based on formal review of the current literature.

Methods: An attempt was made to identify all English and non–English-language articles in which G. biloba extract was given to subjects with dementia or cognitive impairment. Inclusion criteria for the meta-analysis were (1) sufficiently characterized patients such that it was clearly stated there was a diagnosis of AD by either Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition, or National Institute of Neurological Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association criteria, or there was enough clinical detail to determine this by our review; (2) clearly stated study exclusion criteria, ie, those studies that did not have stated exclusions for depression, other neurologic disease, and central nervous system–active medications were excluded; (3) use of standardized ginkgo extract in any stated dose; (4) randomized, placebo-controlled and double-blind study design; (5) at least 1 outcome measure was an objective assessment of cognitive function; and (6) sufficient statistical information to allow for meta-analysis.

Results: Of more than 50 articles identified, the overwhelming majority did not meet inclusion criteria, primarily because of lack of clear diagnoses of dementia and AD. Only 4 studies met all inclusion criteria. In total there were 212 subjects in each of the placebo and ginkgo treatment groups. Overall there was a significant effect size of 0.40 ($P < .0001$). This modest effect size translated into a 3% difference in the Alzheimer Disease Assessment Scale–cognitive subtest.

Conclusions: Based on a quantitative analysis of the literature there is a small but significant effect of 3- to 6-month treatment with 120 to 240 mg of G. biloba extract on objective measures of cognitive function in AD. The drug has not had significant adverse effects in formal clinical trials but there are 2 case reports of bleeding complications. In AD, there are limited and inconsistent data that preclude determining if there are effects on noncognitive behavioral and functional measures as well as on clinician’s global rating scales. Further research in the area will need to determine if there are functional improvements and to determine the best dosage. Additional research will be needed to define which ingredients in the ginkgo extract are producing its effect in individuals with AD.

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METHODS

We attempted to identify all randomized placebo-controlled clinical trials (both English and non-English language) in which G. biloba was administered for at least 2 months to patients with dementia or other cognitive impairment. The search for potentially relevant studies and reviews was performed through MEDLINE using the keywords “ginkgo” and “gingko [sic].” Trials referenced by articles that were found were also screened. Additionally, we had access to a listing of 60 articles with English summaries from a preliminary Cochrane Collaboration Review (http://www.cochrane.co.uk) on the use of ginkgo in dementia and related disorders. This search was done using several databases including MEDLINE, EMBASE, and PsycLit as well as references in review articles and textbooks. Additional search words included brand names for ginkgo (eg, Tanakan, Tebonin, Rokan, or Ginkoba) and a standardized extract, EGB 761. Our goal was to evaluate only those studies that met minimally acceptable scientific standards. We therefore used the following criteria for inclusion in the quantitative review.

- Patients needed to be clearly and sufficiently characterized such that there was a clearly stated diagnosis of AD by either Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition or National Institute of Neurological Disorders and Stroke—Alzheimer’s Disease and Related Disorders Association criteria, or there was enough clinical detail to determine this by our review.
- Studies needed to clearly state their exclusion criteria, ie, those studies that did not have stated exclusions for depression, other neurologic disease, and central nervous system–active medications were excluded. We did not exclude trials solely for the lack of neuroimaging studies on all subjects.
- The use of standardized ginkgo extract in any stated dose was required (24% or 25% ginkgoflavone glycosides and 6% terpenoids, see above). The dose could be given by any route of administration.
- The study needed to be randomized, placebo-controlled, and double-blind. Details of the randomization procedure were not required.
- At least 1 outcome measure needed to be an objective assessment of cognitive function.

The studies that met these inclusion criteria are listed in Table 1. Studies also needed to include descriptive statistics from which effect sizes could be computed. This only caused the exclusion of 1 article in Table 1 from the quantitative analysis.

Meta-analytic methodology was used to quantitatively assess the effects of ginkgo on objective measures of cognition for all studies that were found to meet the above-listed criteria. This statistical methodology involves computation of individual effect sizes for each study sample which, after weighting for sample size, becomes a single case to be used in subsequent analyses. For each evaluated study we computed the effect size (g statistic) according to the methodology of Hedges and Olkin. An initial report suggested that lissencephaly, a disorder of neural migration and dendritic branching, was associated with changes in the gene coding a PAF inactivating enzyme found in cerebral cortex, PAF acetylhydrolase. This was not confirmed in a later independent laboratory study.

The other major components of ginkgo extract are the flavonoids that contribute to ginkgo’s antioxidant and free radical scavenger effects. Ginkgo has been found to (1) reduce cell membrane lipid peroxidation in experimental spinal cord injury similarly to methylprednisolone; (2) reduce bromethalin-induced cerebral lipid peroxidation and edema; (3) protect brain neurons against oxidative stress induced by peroxidation; (4) decrease neuronal injury following ischemia or electroconvulsive shock; and (5) reduce subchronic cold stress effects on receptor desensitization.

Other biological effects of G. biloba extract have been observed. It is an inhibitor of monoamine oxidase A and B. Biological effects in various mammalian species have been demonstrated in many organs, such as decreasing retinal neovascularization following injury, altering the immune system and promoting compensation from vestibular deafferentation.

Therapeutically, ginkgo may be biologically plausible to use in Alzheimer disease (AD) for several reasons. While the cause and underlying pathophysiological features of AD are unknown, prominent hypotheses as to the cause center around age-related oxidative injury. As described earlier, the flavonoid components of ginkgo appear to be useful in animal models in preventing some types of oxidative and peroxidative neuronal injury. Another hypothesis of a cause of AD centers around an inflammatory process. Ginkgo being a PAF antagonist has anti-inflammatory effects. Another reason for the plausibility of use of ginkgo in individuals with AD also relates to its activity as a PAF antagonist. The effect of PAF antagonism directly on brain function is fairly unexplored.

Ginkgo has been widely used by naturopathic doctors and other alternative and complementary health care providers. Alternative or complementary medicine is widely used in North America with 34% of US adults interviewed in 1990 having used some form of alternative medicine in the past year. In the United States people spend an estimated $1.5 billion per year on herbal medicines with projected annual growth of 15%. Germany is one of the largest herbal users among American or western European countries with total sales in 1993 of $1.9 billion for plant-based allopathic medicines (half of these prescribed by physicians) and with 5 million prescriptions for ginkgo in 1988. Clinically, ginkgo extract is widely used in Europe for treatment of memory disorders associated with aging, including AD and vascular dementia. It is already widely used in the United States as an alternative therapy for AD despite the presence of only 1 American study. Prior to the publication of that American trial, a conservative estimate at a university cognitive assessment clinic found 10% of patients using alternative medicines to improve cognitive function and an additional 29% to improve general health. A less conservative estimate comes from another study.

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Fifty-seven articles were identified, of which seven were review articles. There were dozens of studies mostly in the French and German literature suggesting the efficacy of ginkgo for the treatment of memory impairment associated with aging but only a limited number were properly blinded and placebo-controlled with well-characterized subjects. Almost all reported positive effects of ginkgo. The overwhelming majority contained the diagnosis of cerebral insufficiency. However, the term cerebral insufficiency is vague and overinclusive with criteria that include depressed mood, fatigue, lack of motivation, dizziness, and tinnitus. Without sufficiently detailed description all articles simply using the diagnosis of cerebral insufficiency were excluded from the meta-analysis. Other potentially relevant studies were excluded for other reasons. Weibrecht and Janssen studied patients with primary degenerative dementia but did not further describe the inclusion or exclusion criteria. The patients in the study of Chartres et al were receiving decreasing doses of neuroleptics and tranquilizers. There was 1 study that otherwise met the inclusion criteria but could not be included in the formal meta-analysis because of a lack of sufficiently descriptive statistics. Four studies were identified that met all criteria (Table 1). These 4 studies included patients with mild or moderate dementia severity. Although 2 of these studies reported additionally on patients with vascular dementia, only groups composed solely of patients diagnosed as having AD were included in the analysis.

### ANALYSIS TECHNIQUES

Of the 4 studies that met criteria, 2 reported means and SDs. For these studies we computed the g statistic based on pooled SDs. Wesnes et al reported statistical analyses that aggregated their multiple cognitive measures across multiple assessments. However, we deemed it more appropriate to calculate the effect size for Wesnes et al by averaging the effect sizes of their multiple cognitive measures reported for their final assessment (12 weeks). To provide more comparable treatment duration and increase total sample size, the intention-to-treat sample of Le Bars et al at 26 weeks was used to calculate the study's effect size. As this study reported means and 95% confidence intervals (instead of SDs or SEs), the 95% confidence interval was used to calculate the SE, which in turn was used to calculate the SD for use in effect size calculation. Hofferberth reported P values for the Mann-Whitney U statistic, but did not report means or SDs. The effect size for the final assessment (12 weeks) was calculated from the reported P value and sample sizes using the formula reported by Hedges and Olkin.

The 4 studies reported analyzable data for 212 patients treated with ginkgo and 212 with placebo. Individual group sample sizes, as shown in Table 2, ranged from 19 to 104. After appropriate weighting for sample size, the mean effect size of the 4 samples was 0.41 (95% confidence interval, 0.22-0.61). This indicates that the weighted mean effect size was equivalent to a little less than half of an SD. There was significant variability in effect sizes (range, 0.1-1.1).

### ADVERSE EFFECTS

In a previous review, no serious adverse effects were noted in any of the older studies and the incidence of significant adverse effects was similar in all placebo-treated...
and ginkgo-treated groups. In the studies we reviewed and the studies in our meta-analysis there were also no significant adverse effects. In all these studies doses have ranged up to 240 mg/d. Ginkgo may prolong the bleeding time and there are 2 case reports of hemorrhage in subjects who were taking ginkgo. A 33-year-old woman had been taking 120 mg of ginkgo for 2 years prior to developing bilateral subacute subdural hematomas without a known history of trauma. Two simultaneously drawn bleeding times were 15 and 9.5 minutes with the upper limit for the laboratory being 9 minutes. One month after stopping ginkgo, 2 simultaneously drawn bleeding times were both 6.5 minutes. A second case report concerned a 70-year-old man who was taking aspirin daily for 3 years following coronary artery bypass surgery. He developed spontaneous bleeding from the iris into the anterior chamber 1 week after beginning 80 mg/d of Ginkoba, a ginkgo extract. Another case report concerned a 72-year-old who developed a small subdural hematoma several months after beginning ginkgo therapy. A final case report was that of a 78-year-old who had been stable receiving warfarin for atrial fibrillation for 5 years with a prothrombin time of 16.9 seconds who presented with a left parietal intracerebral hemorrhage 2 months after beginning ginkgo therapy. These case reports are clearly of concern. However, given the large but unknown number of people taking ginkgo and the lack of such serious adverse effects reported in any of the published articles to date totaling several thousand subjects, the incidence of bleeding complications with administration of ginkgo is of unknown magnitude and significance.

NEUROPHYSIOLOGY

Several studies on AD have included neurophysiological outcome measures. The trial by Kanowski et al performed electroencephalographic frequency analysis in 36 of the subjects (17 ginkgo-treated and 19 placebo-treated subjects) enrolled at one site and found significant improvement in several electroencephalographic variables in the ginkgo group, including greater dominant posterior frequency and less theta activity. Hofferberth also found a significant decrease in the theta/alpha ratio in the active group compared with the placebo group. Rai et al reported a decrease in slow frequency activity in the treatment group.

Despite the widespread use of G biloba and more than 50 publications on its use in age-related functional and cognitive changes, there are only a handful of randomized, well-controlled studies of its use in patients with a diagnosis of AD. We identified only 1 article before 1991 that met inclusion criteria. This is consistent with the study by Kleijnen and Knipschild who reviewed 40 studies through 1991 concerning the use of G biloba for dementia and cerebral insufficiency. Among the 40 studies, 8 were chosen to meet certain criteria for a good study (a subset of our criteria) and were discussed in more detail in a later article. None of these 8 articles specifically stated that the diagnosis was AD. A single article among 8 had sufficient description such that the diagnoses were determined to be probable AD and it is included in our meta-analysis. The other 7 articles and most of the clinical articles published since, especially the non–English-language articles, do not have sufficiently stringent inclusion criteria with cerebral insufficiency the most common diagnosis.

While all studies can be criticized for some aspects of design and analysis, we believe that 4 studies meet reasonable criteria for an adequate clinical trial in AD. There are some concerns regarding the performance of the studies as well as the quantitative analysis. The studies varied in length of treatment and daily dose of ginkgo (120 or 240 mg). The correct dose of ginkgo has never been formally established. While 120- and 240-mg/d doses are typical among clinical trials, animal studies have used doses of 100 mg/kg. The dose issue will need to be addressed in future studies. The dropout rate in the study of Le Bars et al at 1 year was fairly high. However, to maintain comparability with the trial durations in the other studies we used the 6-month intention-to-treat data from the study of Le Bars et al. The 6-month data did not have a particularly high dropout rate. The outcome measures are of variable quality with only 1 using the Alzheimer Disease Assessment Scale–cognitive subtest (ADAS-cog). However, the Syndom Kurztest is a short neuropsychological battery with high reliability that is similar to the ADAS-cog.

While the small number of trials is a limitation of this meta-analysis, the aggregate sample is fairly large. Despite the heterogeneity among study results, the similarity of effect sizes of the 2 largest studies accounting for more than 75% of the sample supports a real effect. Additionally, the fairly low effect size in the study by Wesnes et al appears to be, at least in part, related to having to average the effect over their 10 outcome measures, some of which would be predicted to be insensitive to intervention. Some of the heterogeneity of effect may be related to dose with the 2 studies using a 240-mg/d dose producing greater effect sizes. Despite all the concerns, the administration of standardized G biloba extract appears to have a modest effect on cognitive function in AD with an effect size of about 0.4. The effect size is comparable with the donepezil trial by Rog-

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| Table 2. Studies Satisfying Inclusion Criteria and With Sufficiently Descriptive Statistics |
|---------------------------------------|----------------|----------------|
| **Source, y** | **Effect Size** | **95% Confidence Interval** | **No. of Subjects** |
| Kanowski et al,86 | 0.5156 | +0.16 to +0.87 | 61 |
| Le Bars et al,24 | 0.311 | +0.04 to +0.59 | 104 |
| Wesnes et al,87 | 0.108 | −0.44 to +0.65 | 26 |
| Hofferberth,81 | 1.117 | +0.45 to +1.78 | 21 |
| Overall | 0.413 | +0.22 to +0.61 | 212 |

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Comment

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preliminary positive results in 2 of the studies\textsuperscript{24,88} for which there is some evidence in vascular dementia, eg, ginkgo in other dementia syndromes, eg, vascular dementia, for which there is some preliminary positive results in 2 of the studies\textsuperscript{24,88} included in our meta-analysis.

The clinical significance of this effect size of about 0.4 is less clear. Not all 4 studies\textsuperscript{21,01,80,87} had functional, behavioral, or global change outcome measures. Since there was an insufficient number for quantitative analysis on these measures, they are briefly summarized herein. The study by Kanowski et al\textsuperscript{80} reported a significant difference in a clinician’s global rating scale but not in an activities of daily living scale. The study by Le Bars et al\textsuperscript{21} reported no significant difference in the clinician’s global rating scale, but did on the Geriatric Evaluation by Relative’s Rating Instrument, their functional scale. Hofferberth\textsuperscript{81} reported improvement in a daily function measure (the Sandoz Clinical Assessment Geriatric Scale). We need further research to determine whether there is improvement in noncognitive behavior or daily function since this is critical in evaluating the use of treatment in AD.

The component of ginkgo extract that produces its clinical effect is not known. If it turns out that the flavonoid components are producing the clinical effect, then other antioxidants may prove as effective and safer. For example, is the effect of ginkgo additive with vitamin E? Alternatively, if the terpenoid components are producing the clinical effect, then it needs to be determined which of the terpenoids is most effective (eg, ginkgolide B). This aspect of ginkgo is potentially of most interest since the unique chemical structure of the terpenoids makes it one of a limited number of good PAF antagonists. The currently available standardized extracts are only standardized to percentage of flavonoids and terpenoids. The implication of this is that the relative amounts of the ginkgolide and bilobalide components of the terpenoids or the various flavonoids may vary across preparations and even seasons.\textsuperscript{94} The individual component chemicals in ginkgo extract, eg, ginkgolide B, are available from some manufacturers.

The enriched or special extract EGB 761 developed by Dr Willmar Schwabe Pharmaceuticals, Karlsruhe, Germany, has been used in most of the trials in Table 1. The patent for extract EGB 761 has expired so other manufacturers can use the same extraction process from the ginkgo leaf. There are no data comparing the efficacy of different formulations of ginkgo in AD, the so-called phytotherapeutic, even though most are standardized to 24% flavonoids and 6% terpenoids.

This article is not intended to produce specific clinical recommendations on the use of ginkgo in individuals with AD. Only additional high-quality research can address this issue. In general, physicians should inquire about alternative therapy use by patients to be aware of potential drug interactions and to ensure that the patient feels comfortable discussing alternative therapies with their nonalternative health care provider. In general, when considering alternative therapies, clinicians should ensure that patients are actually taking what is recommended. Some of the products are not pharmacy grade, do not contain known amounts of the intended drug, and may contain unknown amounts of other compounds. If considering the use of ginkgo, ensure that a standardized extract (24% flavonoids or ginkgo-flavone-glycosides and 6% terpenoids) is used. Given its mode of action on PAF and the case reports of possible hemorrhagic complications, it certainly seems prudent to be cautious in its use in patients taking anticoagulants or antiplatelet agents, or with a bleeding diathesis.

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