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File: ■ Ginkgo (*Ginkgo biloba*)
■ Dementia
■ Cognitive Impairment

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RE: Systematic Review and Meta-analysis of Ginkgo in Dementia

Weinmann S, Roll S, Schwarzbach C, Vauth C, Willich SN. Effects of *Ginkgo biloba* in dementia: systematic review and meta-analysis. *BMC Geriatr*. 2010;10:14. DOI:10.1186/1471-2318-10-14.

Ginkgo (*Ginkgo biloba*) extract EGb 761 is used to treat dementia and cognitive impairment. It is one of the most well studied herbal extracts. Published results have been inconsistent in regards to the efficacy of the extract. Analyses of studies have revealed methodological limitations, small cohorts, and include various dementia subtypes (e.g., vascular dementia, Alzheimer's disease, mild cognitive impairment). The authors point out that most studies subtype the participants, whereas most dementia drugs, including EGb 761, are prescribed without a comprehensive assessment of the patient's dementia subtype. Therefore, the authors conducted a systematic review of the effects of ginkgo on various types of dementia.

The following databases were searched: MEDLINE (January 1, 1966 to August 2008), EMBASE (January 1, 1980 to August 2008), PsycINFO (January 1, 1982 to August 2008), CINAHL (Cumulative Index to Nursing and Allied Health Literature), the Cochrane Database of Systematic Reviews, and the Cochrane Controlled Trials Register (until Issue 3, 2008). The following search terms were used: dementia, senile, Alzheimer, cognition, memory, decline, impair, loss, diminish, ginkgo, bilobalide, Tebonin, EGb 761, and LI1370. The manufacturer of EGb 761, Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany, was queried for additional information. Reference lists were hand searched. Study inclusion criteria included controlled clinical trials, with or without randomization, and studies that assessed people with a confirmed diagnosis of Alzheimer's disease, vascular dementia, or mixed dementia, according to internationally valid diagnostic criteria. Standardized *Ginkgo biloba* extracts needed to be used for at least 12 weeks, and there had to be ≥ 10 patients per treatment group. Studies were excluded if they contained mostly patients with non-vascular or non-Alzheimer's dementia, such as Lewy-body dementia or dementia due to Parkinson's disease. The article had to be published in English, German, French, Italian, or Spanish. The publication quality was assessed. When possible, the data were pooled for a meta-analysis. To increase the power of the meta-analysis, values of different outcome scales

of the same domain were pooled (i.e., data from 2 different measures of cognition were pooled).

Of 754 clinical publications located, only 17 publications, which reported on 9 studies, met all of the inclusion criteria. All 9 studies were randomized, double-blind, and had moderate to good methodological quality. Eight of the studies were placebo-controlled, and 1 compared ginkgo with donepezil. All used EGb 761 (120 mg, 160 mg, or 240 mg per day). Two studies were performed in Germany, 2 in the USA, 2 in the Ukraine, 1 in Bulgaria, 1 in the Netherlands, and 1 in Great Britain. Together the studies included 2372 patients with mild to moderate Alzheimer's disease, vascular dementia, or mixed dementia.

Cognition was evaluated in all 9 studies. The meta-analysis showed that EGb 761 was statistically significantly superior to placebo in improving cognition for the whole group of patients with dementia (i.e., no subgroup analysis of dementia subtype) ($P < 0.04$). In a subgroup analysis of 6 studies that included patients with Alzheimer's disease, EGb 761 treatment was statistically superior to placebo treatment in that population ($P = 0.02$).

Eight of the 9 studies evaluated Activities of Daily Living (ADL). For the whole group of patients, the difference in ADL between placebo and ginkgo treated patients was not statistically significant. However, a subgroup analysis of patients with Alzheimer's disease (5 studies) showed that ginkgo treatment significantly improved ADL compared with placebo treatment ($P = 0.008$).

Neuropsychiatric symptoms were assessed in 7 studies. In some of these studies, only depressive symptoms, which were hardly above the normal range, were monitored. The authors note that based on the results of 2 studies which used the full Neuropsychiatric Inventory, psychological or behavioral symptoms associated with dementia may improve with ginkgo use ($P < 0.05$ versus placebo).

Quality of life was assessed in 3 studies: 2 with no EGb 761-associated improvement, and 1 with a significant improvement with EGb 761. A subgroup analysis indicates that a dose of 240 mg may be necessary for clinically relevant improvements in quality of life. The authors conclude that additional quality of life data are needed.

The results of 9 studies indicate that EGb 761 was well tolerated. The number and type of adverse events and study withdrawals were similar between EGb 761 and placebo treated patients. However, randomized controlled trials do not evaluate drug interactions and rare events, so these parameters could not be assessed. Also, only 1 ginkgo product was used in all 9 studies, so other ginkgo products could be associated with different adverse side effects. Mild gastrointestinal symptoms, headache, dizziness, or allergic skin reactions have been reported with EGb 761 use. Occasional reports of bleeding have been reported in patients using ginkgo preparations. However, studies show that EGb 761 does not influence blood clotting, bleeding times, or potentiate the effects of anticoagulant or antiplatelet drugs.

The results of this meta-analysis are consistent with the Cochrane analysis, which indicates a small advantage of ginkgo compared with placebo at 12 and 24 weeks. The difference between the 2 analyses are (1) the present meta-analysis only included studies where patients had a validated dementia diagnosis; this was not an inclusion criterion of the Cochrane analysis, (2) there was a higher methodological quality of the

studies included in the present meta-analysis, (3) the present meta-analysis included 3 newly published studies, and (4) values of different outcome scales of the same domain were pooled in the present meta-analysis.

The authors conclude that the duration of a study, the study setting, and methodological design factors may strongly modify the study outcome. The generalizability of the various studies, and of this meta-analysis, may be limited. The studies excluded patients with severe somatic or psychiatric comorbidities. Use of other medications was restricted. One study showing a lack of ginkgo efficacy included only patients living in old people's homes and included mostly very old people. The meta-analysis only included 1 type of ginkgo extract.

Overall, the statistical effect size of EGb 761 treatment was moderate, but the clinical relevance is generally difficult to determine. The clinical significance of pharmaceuticals used to treat dementia is difficult to measure. Nonetheless, based on the data and ginkgo usage patterns, the authors believe that ginkgo may be beneficial for "a certain but unknown proportion of dementia patients." The disparity in outcomes between studies is not fully explained by dementia type or ginkgo dose. The authors "think that the hitherto gained results justify both symptomatic treatment of dementia and further research."

—Heather S. Oliff, PhD

Enclosure: Referenced article is an Open Access article via BioMed Central.