

COCHRANE FOR CAM PROVIDERS: EVIDENCE FOR ACTION

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Clinical scenario: A 67-year-old man presents with progressive development of symptoms of memory loss, apathy, decreased judgment, and change in mood during the past year. After physical examination and appropriate laboratory tests by a doctor, the patient in question is diagnosed with mild dementia and cognitive impairment, excluding organic or arteriosclerotic disorders. The patient would like to try phytotherapy and asks if herbal remedies might improve his condition. The provider searches *The Cochrane Library* and identifies the potentially relevant review “*Ginkgo biloba* for cognitive impairment and dementia,” an abstract of which follows.

ABSTRACT

Background

Extracts of the leaves of the maidenhair tree, *Ginkgo biloba*, have long been used in China as a traditional medicine for various disorders of health. A standardized extract is widely prescribed in Germany and France for the treatment of a range of conditions, including memory and concentration problems, confusion, depression, anxiety, dizziness, tinnitus, and headache. The mechanisms of action are thought to reflect the action of several components of the extract and include increasing blood supply by dilating blood vessels, reducing blood viscosity, modification of neurotransmitter systems, and reducing the density of oxygen free radicals.

Objectives

The aim of the review is to assess the efficacy and safety of *Ginkgo biloba* for the treatment of patients with dementia or cognitive decline.

Search Strategy

Trials were identified on 26 June 2002 through a search of the CDCIG Specialized Register, which contains records from all main medical databases (MEDLINE, EMBASE, CINAHL, PsycINFO, SIGLE, LILACS), from ongoing trials databases such as Clinicaltrials.gov and Current Controlled Trials and many other sources. The search terms used were ginkgo*, tanakan, EGB-761, EGB761 and “EGB 761.”

Selection Criteria

All relevant, unconfounded, randomized, double-blind controlled studies, in which extracts of *Ginkgo biloba* at any strength and over any period were compared with placebo for their effects on people with acquired cognitive impairment, including dementia, of any degree of severity.

Data collection and analysis

Data for the meta-analyses are based on reported summary statistics for each study. For the intention-to-treat analyses, we sought data for each outcome measure on every patient randomized, irrespective of compliance. For the analyses of completers we sought data on every patient who completed the study on treatment.

For continuous or ordinal variables, such as psychometric test scores, clinical global impression scales, and quality of life scales, there are two possible approaches. If ordinal scale data appear to be approximately normally distributed, or if the analyses reported by the investigators suggest that parametric methods and a normal approximation are appropriate, then the outcome measures will be treated as continuous variables. The second approach, which may not exclude the first, is to concatenate the data into two categories which best represent the contrasting states of interest, and to treat the outcome measure as binary. For binary outcomes, the endpoint itself is of interest and the Peto method of the typical odds ratio is used.

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Main Results

Overall, there are no significant differences between *Ginkgo* and placebo in the proportion of participants experiencing adverse events. Most studies report the analyses of data from participants who completed the treatment; there are few attempts at ITT analyses. Therefore we report completers' analyses only. The clinical global improvement scale, measuring clinical global improvement as assessed by the physician, was dichotomized between participants who showed improvement and those who were unchanged or worse. There are benefits associated with *Ginkgo* (dose less than 200mg/day) compared with placebo at less than 12 weeks (54/63 showed improvement compared with 20/63, OR 15.32, 95% CI 5.90 to 39.80, $P < .0001$), and *Ginkgo* (dose greater than 200mg/day) at 24 weeks (57/79 compared with 42/77, OR 2.16, 95% CI 1.11 to 4.20, $P = .02$).

Cognition shows benefit for *Ginkgo* (dose less than 200mg/day) compared with placebo at 12 weeks (SMD -0.57, 95% CI -1.09, -0.05, $P = 0.03$, random effects model), *Ginkgo* (greater than 200 mg/day) at 12 weeks (SMD -0.56, 95% CI -1.12 to -0.0, $P = 0.05$), at 12 weeks (*Ginkgo* any dose) (SMD -0.71, 95% CI -1.23 to -0.19 $P = 0.008$, random effects model) at 24 weeks (*Ginkgo* any dose) (SMD -0.17, 95% CI -0.32 to -0.02 $P = 0.03$) and at 52 weeks (*Ginkgo* less than 200 mg/day) (SMD -0.41, 95% CI -0.71 to -0.11, $P < .01$).

Activities of Daily Living (ADL) shows benefit for *Ginkgo* (dose less than 200mg/day) compared with placebo at 12 weeks (SMD -1.10, 95% CI -1.79, -0.41, $P < .01$), *Ginkgo* (dose less than 200 mg/day) at 24 weeks (SMD -0.25, 95% CI -0.49 to -0.00, $P = .05$), and at 52 weeks (*Ginkgo* less than 200 mg/day) (SMD -0.41, 95% CI -0.71 to -0.11, $P < .01$).

Measures of mood and emotional function show benefit for *Ginkgo* (dose less than 200 mg/day) compared with placebo at less than 12 weeks (SMD -0.51, 95% CI -0.99 to -0.03, $P = .04$) and *Ginkgo* (dose less than 200mg/day) at 12 weeks (SMD -1.94, 95% CIs -2.73, -1.15 $P < .0001$).

There are no significant differences between *Ginkgo* and placebo in the proportion of participants experiencing adverse events. There are no data available on Quality of Life, measures of depression or dependency.

Reviewers' conclusions

Ginkgo biloba appears to be safe in use, with no excess side effects compared with placebo. Many of the early trials used unsatisfactory methods, were small, and we cannot exclude publication bias. Overall there is promising evidence of improvement in cognition and function associated with *Ginkgo*. However, the three more modern trials show inconsistent results. There is need for a large trial using modern methodology and permitting an intention-to-treat analysis to provide robust estimates of the size and mechanism of any treatment effects.

This review should be cited as:

Birks J, Grimley Evans J, Van Dongen M *Ginkgo Biloba* for

Cognitive Impairment and Dementia (Cochrane Review). In: *The Cochrane Library*, Issue 4, 2003. Chichester, UK: John Wiley & Sons, Ltd.

Does this review address an important clinical question?

The objective of this systematic review is to "assess the efficacy and safety of *Ginkgo biloba* for the treatment of patients with dementia or cognitive decline." Given the widespread use of this complementary medicine, this question is pertinent and is relevant to the patient's needs.

Were the criteria for inclusion of studies clearly described and fairly applied?

This review has clear inclusion criteria. It includes randomized, double-blind, controlled trials that compare *Ginkgo biloba* to placebo in people with dementia or cognitive impairment. The outcomes measured are clinically relevant, including efficacy, acceptability, and safety. The reviewers have applied these criteria to all the potentially relevant studies and have given specific reasons for excluding some studies. However, it would be useful to have information about the relative benefit of *Ginkgo biloba* compared to conventional treatment, other herbal remedies, and no treatment.

Was the search for studies thorough?

One of the big differences between traditional narrative reviews and systematic reviews is that systematic reviews use a comprehensive search to find all relevant studies. The range of databases and trial registers searched, the dates of the searches, the search terms used, as well as the permitted publication languages and publication status, are important components of such a search strategy.

The reviewers searched the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group, which contains records from the main trial registers (CENTRAL) and medical electronic databases (for example MEDLINE, EMBASE, and CINAHL); these sources were searched from their inception until shortly before the review was published. The reviewers also contacted companies that manufacture *Ginkgo biloba* preparations. The search terms are appropriate. The reviewers do not clearly state whether they attempted to locate studies regardless of language; for example, did they attempt to translate studies that were not published in English? It is also unclear whether the reviewers searched for unpublished or ongoing trials in addition to published trials. Sometimes studies that show an intervention to be ineffective remain unpublished; this is an example of publication bias,¹ which reviewers should address by attempting to locate both published and unpublished studies.

Was the study quality assessed?

Less rigorous trials tend to overestimate the effectiveness of therapeutic interventions.² In this case, the reviewers only included double-blind randomized controlled trials. They

assessed the methodological quality of these trials in terms of design, assessment of outcomes, and completion rate. The reviewers do not mention allocation concealment—the “process used to prevent foreknowledge of group assignment in a randomized controlled trial”³—in their assessment of methodological quality. However, a table in the published full review shows that it is adequate in only 14 of the included trials and unclear in the remaining 19 trials.

Were the treatment effects similar and the summarized results valid?

The results showed benefits associated with *Ginkgo biloba* compared to placebo in terms of clinical global improvement (CGI), cognition, activities of daily living (ADL), and mood and emotional function. It is unclear why mood and emotional function have been analyzed since neither of these are pre-specified outcomes. For some of the outcomes, the effects were similar among the trials (eg, CGI), but other effects were not consistent among trials (eg, cognition). The variation in cognition outcome was explained as resulting from inconsistent measurements in aspects of cognition. No trial provided data on quality of life, or measures of depression or dependency.

Although only one of the trials had “adverse effects” as an outcome (as described in the ‘Characteristics of included studies’), the reviewers present adverse effect data from 15 trials. An explanation of this discrepancy would be helpful.

Typically, meta-analyses weight studies according to their size and quality. The reviewers state that the efficacy of *Ginkgo biloba* would be modified to report less benefit if they omitted a study that used poor methods. This could have been demonstrated to readers had the reviewers conducted a sensitivity analysis, in which trials with poor methodological quality were excluded.

Are the recommendations based firmly on the quality of the evidence presented?

In the Reviewers’ conclusions, several shortcomings were mentioned, such as, methodological flaws, small size, potential publication bias, and inconsistent findings from recent trials. The potential benefit needs to be investigated in large, rigorous trials.

Resolution

Systematic reviews that summarize scientific evidence are useful for clinicians trying to make decisions.⁴ In this review, the evidence for the benefit of *Ginkgo biloba* to improve cognition and function appears promising but not conclusive. Some studies included patients with different types of dementia, as well as people with cognitive impairment. There was also variation in the doses used in the studies (from 112 to 240 mg/day) and treatment duration (<12 to 52 weeks). The provider could inform the patient about the possible benefit and harm, and ask his preference for treatment. We suggest that the doctor inform the patient about available conventional therapies such as amitriptyline⁵ (as *Ginkgo biloba* should be

also compared to conventional therapy). The provider could also inform the patient about other herbal therapies, such as St John’s Wort (herb hypericum), which is more effective than placebo for short-term treatment of mild to moderately severe depressive disorders.⁶

CONCEPTS IN STUDY DESIGN

Meta-analysis, odds ratio, relative risk, confidence interval, standardized mean difference, intention to treat analysis

Meta-analysis

Meta-analysis is the use of statistical technique to combine the results of two or more studies.⁷ Meta-analysis confers more power to detect small but clinically significant effects by drawing on data from many trials.

Odds ratio

Odds Ratio (OR) is an outcome measure of the effect of a treatment. OR represents the ratio of the odds of an event in the experimental group to the odds of an event in the control group.⁷ Thus, if a group of 100 people had an event rate of 0.20, 20 people had the event and 80 did not, and the odds would be 20/80 or 0.25. An odds ratio of 1 indicates no difference between comparison groups. For undesirable outcomes an OR that is < 1 indicates that the intervention was effective in reducing the risk of that outcome. When the event rate is small, OR is very similar to relative risk.

Relative risk

Relative Risk (RR) represents the ratio of risk in the experimental group to the risk in the control group.⁷ The risk is the ratio of people with an event in a group to the total in the group. A RR of 1 indicates no difference between comparison groups. For undesirable outcomes a RR that is < 1 indicates that the experimental intervention was effective in reducing the risk of that outcome.

Confidence interval

Confidence Interval (CI) represents a measure of the precision (or uncertainty) around an effect estimate of treatment for making inferences about the population.⁸ It is a range of values either side of the estimates in which we can be 95% sure that the true value lies (sometimes other percentages such as 90% or 99% are used). CI indicates the strength of evidence about magnitude of treatment benefit.

Standardized mean difference

The Standardized Mean Difference (SMD) is the difference between two means divided by an estimate of the within-group standard deviation.⁷ When an outcome (such as pain) is measured in a variety of ways across studies (using different scales) it may not be possible to directly compare or combine study results in a systematic review. By expressing the effects as a standardized value the results can be combined since they have no units.

Intention-to-treat analysis

The Intention-to-treat (ITT) analysis is a method that analyzes the results according to the treatment to which people were allocated instead of the treatment they actually received.⁷

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