Ginkgo Biloba for cognitive impairment and dementia (Review)

Birks J, Grimley Evans J

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2002, Issue 4

http://www.thecochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Ginkgo Biloba for cognitive impairment and dementia

J Birks, J Grimley Evans

Contact address: Mrs Jacqueline Birks, Coordinating Editor CDCIG, Department of Clinical Geratology, University of Oxford, Radcliffe Infirmary, Woodstock Road, Oxford, OX2 6HE, UK. jacqueline.birks@geratology.ox.ac.uk.

Editorial group: Cochrane Dementia and Cognitive Improvement Group.
Publication status and date: Commented, published in Issue 1, 2007.

Citation: Birks J, Grimley Evans J. Ginkgo Biloba for cognitive impairment and dementia. *Cochrane Database of Systematic Reviews* 2002, Issue 4. Art. No.: CD003120. DOI: 10.1002/14651858.CD003120.

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, modificaton 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.

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 CGI 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.

Authors' 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.

PLAIN LANGUAGE SUMMARY

Some evidence of the efficacy of ginkgo biloba for dementia and cognitive impairment.

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.

BACKGROUND

Medicinal products derived from the maidenhair tree, Ginkgo biloba, are some of the most widely used of any plant-based products. There is much literature devoted to Ginkgo biloba, and it has been investigated in many clinical trials. Many excellent reviews covering different aspects of Ginkgo biloba have been writ-

ten (Chang 1997; De Feudis 1998; Curtis 1999; Massey 1999; Van Dongen 2000) and a summary of these provides a comprehensive background.

The tree, from the genus Ginkgo, probably originated in China and is believed to be the oldest living tree species. It grows to a height of about 30 m and can survive for 1000 years. The leaf shape, with two lobes (biloba) is distinctive and unusual. The trees are dioecious (separate male or female) . It is an extremely robust tree, resisting insect and fungus attack, and survives frosts. The tree is now cultivated in many parts of the world for the exploitation of the medicinal properties of its leaves. There are large commercial plantations in Western France, South Carolina, USA, Japan, Korea and China, and these provide enough leaves to satisfy demand.

The active components of Ginkgo biloba consist of flavonoids, terpenoids, and terpene lactones (ginkgolides and bilobalide). These are the compounds found extensively in plants except for the ginkgolides and bilobalide, which are unique to Ginkgo biloba. A well-defined extract , EGb 761, is produced from the ground-up leaves which contains 24% w/w (weight of active compound / total weight of extract) flavone glycosides and 6% w/w terpene lactones. It is marketed as Tanakan, Tebonin, Rökan. Kaveri (LI 1370) is similar but with 25% w/w glycosides. EGb 761 is one of the top five prescription medicines in Germany. Ginkgo biloba is available without prescription in the UK , Canada and the USA where it is marketed as a food supplement.

Ginkgo biloba has been used in China as a traditional medicine for a range of conditions, including asthma, bronchitis, heart dysfunction, for at least 5000 years. Dr Schwabe introduced Ginkgo biloba into Germany in 1965 where it is prescribed extensively for cerebral insufficiency, a diagnosis that can cover a range of conditions including memory and concentration problems, confusion, depression, anxiety, dizziness, tinnitus and headache. This use extends to France, but not to other European countries or the USA. It may protect neuronal and myocardial cells against ischaemia and reperfusion injury. It is believed that the medicinal properties of Ginkgo biloba are due to a combination of effects and that it acts by increasing blood supply by dilating blood vessels, reducing blood viscosity, by modificaton of neurotransmitter systems, and by reducing the density of oxygen free radicals. Its effect on blood clotting is controversial; one of its components Ginkgolide B is an inhibitor of platelet-activating factor and there have been isolated case reports of subdural haematoma associated with high doses (Rowin 1996) and of hyphema (spontaneous bleeding into the anterior chamber of the eye) following combined therapy with Ginkgo extract and aspirin (Rosenblatt 1997). Specific studies have been reported that show no consistent effect of EGb 761 on blood clotting or bleeding time (R. Hoerr personal communication) .

The main use of Ginkgo biloba is in the treatment of cerebral dysfunction. Ginkgo biloba is recommended for age-related cognitive decline and for slowing the progress of neurodegenerative disorders such as Alzheimer's disease and for other forms of dementia. Many clinical trials have been conducted to assess these potential properties and several reviews of the results have been published (Warburton 1986; Kleijnen 1992; Hopfenmüller 1994; Knipschild 1994; Oken 1998; Søholm B 1998; Ernst 1999) but there is still no compelling evidence of the efficacy of Ginkgo biloba for cerebral function. New trials to assess the efficacy of Ginkgo biloba compared with placebo for dementia and cognitive decline are still being initiated.

OBJECTIVES

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

RESULTS

Overall, there are no significant differences between Ginkgo and placebo in the proportions of participants dropping out before the scheduled end of treatment.

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 CGI 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).

Several rating scales, or sub-tests from rating scales were used to assess cognition. Some tests assessed only one or two aspects of memory or cognition (Wesnes 1987 Wechsler digit span; Weitbrecht 1985, Wechsler digit symbol; Mancini 1993, The Toulouse - Pieron Cancellation Test; Hofferberth 1989, The Vienna Reaction Test; Graessel 1992, speed of learning test; Vorberg 1989, Crichton memory impairment sub-test; Brautigam 1998, EMCT attention and concentration) and others assessed a range of functions of cognition (Winther 1998, Wechsler memory function; Maurer 1997 and Van Dongen 2000, SKT; Le Bars 1997, ADAS-cog). The results of the meta-analyses of the 12-week data indicate heterogeneity between the studies. This may be due to the wide variation in outcome measures which are not assessing the same aspects of cognition. This has to be considered when interpreting the results.

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 were no data available on Quality of Life, measures of depression or dependency.

DISCUSSION

1. It is difficult to carry out subgroup analyses based on diagnostic categories. Although some trials appear to exclude all except a specific category, such as Alzheimer's disease, most trials have a mixture of categories either by choice or because standardized criteria were not available for more precise diagnoses. The percentages in each category are usually unknown, and, except for two trials, results are not reported separately for each category. Already faced with a situation where many results are not in the meta-analyses because they were not reported with sufficient detail, a subgroup analysis based on diagnostic category would not be informative.

2. We have listed a group of studies that diagnose and assess patients using a list of typical symptoms. The methods, reporting and analyses are unsatisafctory and most of this information could not be included in meta-analyses. It is interesting to note that all of these studies report highly significant benefit for Ginkgo compared with placebo.

3. The more recent studies might be expected to provide more reliable results owing to improved methodology and larger size. Unfortunately Oswald 1997does not report results with sufficient detail. Oswald 1997 reports only the numbers of responders, where a responder is defined as someone who shows improvement compared with baseline. Absolute values of treatment effects are superior to an arbitrary concept of response that loses so much precision. Dr Willmar Schwabe Pharmaceuticals is still considering our request for access to company reports of this study so that it can contribute to the meta-analyses. We have already discussed the problems with Le Bars 1997. If this study were omitted from the analyses our conclusions concerning the efficacy of Ginkgo would be modified to report less benefit. Brautigam 1998 shows far less benefit associated with Ginkgo than do the earlier studies, (albeit with much lower dosages) and Van Dongen 2000 shows none at all.

4. Two of the earliest studies, Allain 1993 and Arrigo 1985 used much higher doses of Ginkgo biloba than the later trials. Unfortunately we have no results to report from these studies. The doses used in the later studies varied from 112 mg/day to 240 mg/day but there is little evidence that the dose made any difference to the results. It is noted that the dose used by Brautigam 1998 is much lower than that used by any other study.

5. We are unable to exclude the possibility of publication bias affecting earlier studies.

There is more to the appraisal of scientific evidence than simply selecting reports on the basis of their published details and feeding the results into meta-analytic software. The systematic review process is insensitive to some sources of bias and will consolidate some others. The rigour with which RCTs are carried out has improved considerably within the memories of doctors who qualified in the 1950s and 1960s, as the underlying logic of randomization has become more widely understood. In the past, the provision of supposedly opaque envelopes allocated according to sequences of random numbers did not necessarily prevent individual clinical characteristics of patients having an effect on their allocation between treatment and placebo groups. This observation carries no implication of conscious or unconscious fraud; it is simply that people did not fully understand the rationale and purpose of the methodology (as distinct from the methods) of clinical trials.. Indeed if this were not so there would have been no need to develop the more modern techniques of randomization by centralized computer systems. Certainly a bald report that a study was "randomized" - sufficient to qualify for inclusion in many systematic reviews - must for early studies at least be associated with a number of reservations. A case could be made for some system of discounting the contribution of earlier trials to a systematic review for the background trend of increasing methodological rigour over the decades. The widespread practice of clinicians preferring the results of a single recent trial to a meta-analysis of previous results has, in part, a rational basis.

In guarding against observer error and placebo effects it is a scientific as well as an ethical requirement that controlled clinical trialshould be carried out by investigators who are genuinely in a state of equipoise in their prior opinion about the efficacy of the treatment under investigation. It is equally important that the

participants should not have prior opinions of the relative likelihood of benefit or harm from the intervention. If we read that participants in a trial can be withdrawn and given the drug under investigation "on humanitarian grounds" if they deteriorate while in a trial, we have to wonder about possible lack of equipoise and the range of effects this might have had on the trial.

One source of disturbance to equipoise is a desire, rather than an expectation, that the treatment should work. This affects both patients and doctors. In addition to clinical compassion there may be professional reasons why a doctor may have a vested interest in conducting a trial with positive, and publishable, results rather than a null, inconclusive or negative one. The strength of this pressure on the doctor may vary with different cultural settings, different healthcare systems, and different ways of funding research. Again it is important to emphasise that we are not talking about fraud, but about the unconscious and often well-intentioned sources of biased observation that the methodology of the randomised controlled trial was created to counter.

Meta-analysis reviews will consolidate the effects of pervasive sources of bias. Best documented is publication bias. Anything short of a miracle drug will generate some null or even negative results in small trials. Registration of trials in progress, and enlightened editorial policies towards publishing non-positive trials, have only in very recent times reduced the risk of publication bias. A dearth of non-positive trial results before such modern safeguards were introduced, especially when trials were normally small, must raise fears that meta-analysis has revealed publication bias rather than a true effect of a treatment. It is possible in some instances to demonstrate the presence of publication bias statistically, but impossible ever to exclude it. Particular concern arises where it is known that a pharmaceutical company has unpublished information about trials in its files that it has not made available for systematic review. The concern has to be that the unpublished material is less encouraging than the published about the efficacy of the company's product. One of the benefits of the Cochrane system has been to put pressure on pharmaceutical companies to make all their data publicly available by drawing attention to the unreliability of reviews where data are being withheld by an interested party.

At another level of concern, is the process whereby a treatment produces an apparently beneficial effect. The hope is to identify treatments that modify the causes or mechanisms of a disease rather than merely its manifestations. As an example, a common feature of dementia is depression of mood. A treatment that improves cognition and functional capabilities may well reduce depression as a secondary effect. However, a treatment with a simple antidepressant action may be expected to improve subjective wellbeing, capability in cognition and activities of daily living, as well as improving scores such as clinical global impression. In terms of clinical significance, however, a drug that helps people with dementia by lightening their depression is in a different category from one that prevents the condition or ameliorates its natural history. Not least there may be more effective and cheaper antidepressant drugs available. The fact that drugs with antidepressant actions may appear to be effective in the short-term treatment of dementia was recognised thirty years ago. It may be that an antidepressant action is one of the mechanisms of the placebo effect in trials of treatments of dementia, particularly where participants and their carers have an underlying expectation of the drug's efficacy. It is noteworthy that Ginkgo appears to have an antidepressant effect, and future trials should seek to separate an antidepressant effect from other possible mechanisms of benefiting cognition. The heterogeneity noted in the results of the various trials could reflect both variation in the diagnoses of patients entered and differential sensitivities of the outcome measures to the various domains of mood and cognitive function.

These are but some of the considerations that reviewers have to bear in mind in forming their personal conclusions about the meaning of the data they have been studying. If the results of a review and meta-analysis could stand alone, Cochrane procedures would not provide for the expression of "Reviewers' conclusions". Reviewers' conclusions are affected by factors such as judgement, experience, and more nebulous factors such as a "feel" of the data and their context. Systematic reviews are not a substitute for thought; the reader must form his or her own opinion about the relative merits of the probability values emerging from the meta-analysis and any reservations implied by the reviewers in their conclusions.

AUTHORS' CONCLUSIONS

Implications for practice

Ginkgo biloba appears to be safe in use with no excess side effects compared with placebo. The percentage of dropouts from the trials is generally low from both placebo and Ginkgo groups. 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. Our view is that 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.

Implications for research

Further clinical trials of Ginkgo biloba in the treatment of acquired cognitive impairment, using modern standardized techniques and of adequate size, are required.

ACKNOWLEDGEMENTS

We are grateful to the Alzheimer Society for financial support for carrying out this review, and for Robert Hörr of Dr. Willmar Schwabe GmbH & Co for answering our questions about the studies and for providing us with translations and reports of studies, and for the contribution of the consumer editor U Hla Htay. Martien van Dongen has been helpful i nthe drafting of the protocol for this review.

REFERENCES

References to studies included in this review

Allain 1993 *{published data only}*

* Allain H, Raoul P, Lieury A, LeCoz F, Gandon JM, d'Arbigny P. Effect of two doses of Ginkgo biloba extract (EGb 761) on the dual-coding test in elderly subjects. *Clinical-Therapeutics:-The-International-Journal-of-Drug-Therapy* 1993;**15**(3):549–58.

Arrigo 1985 *{published data only}*

Arrigo A, Cattaneo S. Clinical and psychometric evaluation of Ginkgo biloba extract in chronic cerebro-vascular diseases. In: Agnoli A, Rapin JR, Scapagnini V, Weitbrecht WV editor(s). *Effacts of Ginkgo biloba extract on organic cerebral impairment*. John Libbey Eurotext Ltd, 1985:85–9.

Arrigo 1986 *{published data only}*

Arrigo A. Behandlung der chronischen zerebrovaskulaeren Insuffizienz mit Ginkgo-biloba-Extrakt. *Therapiewoche* 1986;**36**:5208–18.

Augustin 1976 *{published data only}*

Augustin P. Le Tanakan en geriatrie. Etude clinique et psychometrique chez 189 malades d'hospice. *Psychologie Medicale* 1976;**8**:123–30.

Brautigam 1998 *{published data only}*

* Brautigam MRH, Blommaert FA, Verleye G, Castermans J, Jansen Steur ENH, Kleijnen J. Treatment of age-related memory complaints with Ginkgo biloba extract: a randomized placebo-controlled study. *Phytomedicine* 1998; **5**(6):425–34.

Brüchert 1991 *{published data only}*

Brüchert E, Heinrich SE, Ruf-Kohler P. Wirksamkeit von LI 1370 bei älteren Patienten mit Hirnleistungsschwäche. Multizentrische Doppelblindstudie des Fachverbandes Deutsche Allgemeinärtze. *Münch. Med. Wochenschr* 1991; **133**:S9–S14.

Chartres 1987 *{published data only}*

* Chartres JP, Bonnan P, Martin G. Dosage reduction in psychotropic medications administered to aged institutionalized patients: A double-blind study with Gingko Biloba extract 761 and placebo [Reduction de posologie de medicaments psychotropes chez des personnes agees vivant en institution. Etude a double–insu chez des patients prenant soit de l'extrait de Ginkgo biloba 761 soit du placebo]. *Psychologie-Medicale* 1987;**19**(8):1365–75.

Eckmann 1982 *{published data only}*

Von Eckmann F, Schlag H. Kontrollierte Doppelblind-Studie zum Wirksamkeitnachweis von Tebonin forte bei patienten mit zerebrovaskulaerer Insuffizienz. *Fortschr. Med* 1982;**100**:1474–8.

Eckmann 1990 *{published data only}*

* Von Eckmann F. Cerebral insufficiency--treatment with Ginkgo-biloba extract. Time of onset of effect in a double-blind study with 60 inpatients [Hirnleistungsstorungen—-Behandlung mit Ginkgo–biloba–Extrakt. Zeitpunkt des Wirkungseintritts in einer Doppelblindstudie mit 60 stationaren Patienten]. *Fortschr Med* 1990;**108**(29):557–60.

Graessel 1992 *{published data only}*

* Graessel E. Effect of Ginkgo-biloba extract on mental performance. Double-blind study using computerized measurement conditions in patients with cerebral insufficiency [Einfluss von Ginkgo–biloba–Extrakt auf die geistige Leistungsfahigkeit. Doppelblindstudie unter computerisierten Messbedingungen bei Patienten mit Zerebralinsuffizienz]. *Fortschr Med* 1992;**110**(5):73–6.

Haase 1996 *{published data only}*

* Haase J, Halama P, Horr R. Effectiveness of brief infusions with Ginkgo biloba Special Extract EGb 761 in dementia of the vascular and Alzheimer type [Wirksamkeit kurzdauernder Infusionsbehandlungen mit Ginkgo–biloba–Spezialextrakt EGb 761 bei Demenz vom vaskularen und Alzheimer–Typ]. *Z Gerontol Geriatr* 1996; **29**(4):302–9.

Horr R, Kieser M. Ginkgo biloba special extract EGb 761--an anti-dementia drug [Ginkgo–biloba–Spezialextrakt EGb 761—-ein Antidementivum]. *Fortschr Med* 1998;**116**(3): 39–40.

Halama 1988 *{published data only}*

* Halama von P, Bartsch G, Meng G. Disorders of brain performance of vascular origin. Randomized double-blind study of the effectiveness of Gingko biloba extract [Hirnleistungsstorungen vaskularer Genese. Randomisierte Doppelblindstudie zur Wirksamkeit von Gingko–biloba–Extrakt]. *Fortschr Med* 1988;**106**(19): 408–12.

Halama 1991 *{published data only}*

Halama P. [Ginkgo biloba. Wirksamkeit eines Spezialextrakts bei Patienten mit zerebraler Insuffizienz].

Munch med Wschr 1991;**133**:190–194.
Halama P. Judgement of well-being and psychometric tests in patients from a neurological proctice treated with Ginkgo [Befindlichkeitsbeurteilung und Psychometrie. testung der Ginkgo–biloba–Wirkung bei Patienten einer Neurologischen Fachpraxis]. *Munch med Wschr* 1991;**133** (Suppl 1):S19–S22.

Hartmann 1991 ***{published data only}***
Hartmann A, Frick M. [Wirkung eines Ginkgo–Spezial–extraktes auf pychometrische Parameter bei Patienten mit vaskulär bedingter Demenz]. *Münch. Med. Wochenschr* 1991;**133**:S23–S25.

Hofferberth 1989 ***{published data only}***
* Hofferberth B. The effect of Ginkgo biloba extract on neurophysiological and psychometric measurement results in patients with psychotic organic brain syndrome. A double-blind study against placebo [Einfluss von Ginkgo biloba–Extrakt auf neurophysiologische und psychometrische Messergebnisse bei Patienten mit hirnorganischem Psychosyndrom. Eine Doppelblindstudie gegen Plazebo]. *Arzneimittelforschung* 1989;**39**(8):918–22.

Hofferberth 1991 ***{published data only}***
Hofferberth B. Ginkgo-biloba-Spezialextrakt bei Patienten mit hirnorganischem Psychosyndrom. Pruefung der Wirksamkeit mit neurophysiologischen und psychometrischen Methoden [Ginkgo biloba Special Extract treatment in patients with cerebro–organic syndrome. Study on the efficacy with neurophysiological and psychometrical methods]. *Munch. Med. Wochenschr* 1991;**133**:S30–S33.

Hofferberth 1994 ***{published data only}***
* Hofferberth B. The efficacy of EGb 761 in patients with senile dementia of the Alzheimer type, a double-blind, placebo-controlled study on different levels of investigation. *HUMAN PSYCHOPHARMACOLOGY* 1994;**9**(3):215–22.

Israel 1987 ***{published data only}***
Deberdt W. Interaction between psychological and pharmacological treatment in cognitive impairment. *Life Sciences* 1994;**55**(26/26):2057–66.
Israel L, Dell'Accio E, Martin G, Hugonot R. Extrait de ginkgo biloba et exercises d'entrainement de la memoire. Evaluation comparative chez des personnes agees ambulatoires. *Pychologie Med* 1987;**19**:1431–9.

Kanowski 1996 ***{published data only}***
Horr R, Kieser M. Ginkgo biloba special extract EGb 761--an anti-dementia drug [Ginkgo–biloba–Spezialextrakt EGb 761—-ein Antidementivum]. *Fortschritte Der Medizin* 1998;**116**(3):39–40.
* Kanowski S, Herrmann WM, Stephan K, Woerich W, Horr R. Proof of efficacy of the ginkgo biloba special extract EGb 761 in outpatients suffering from mild to moderate primary degenerative dementia of the Alzheimer type or multi-infarct dementia. *Pharmacopsychiatry* 1996;**29**(2): 47–56.

Le Bars 1997 ***{published data only}***
* Le Bars PL, Katz MM, Berman N, Itil TM, Freedman AM, Schatzberg AF. A placebo-controlled, double-blind, randomized trial of an extract of Ginkgo biloba for dementia. North American EGb Study Group [see comments]. *JAMA* 1997;**278**(16):1327–32.
Le Bars PL, Kieser M, Itil KZ. A 26-week analysis of a double-blind, placebo-controlled trial of the Ginkgo biloba extract EGb 761 in dementia. *Dementia and Geriatric Cognitive Disorders* 2000;**11**(4):230–7.
Por CP, Evans MF. Does ginkgo help delay dementia?. *Can Fam Physician* 1998;**44**:997–9.
Stevermer JJ, Lindbloom EJ. Clinical question: Does an extract of Ginkgo biloba safely alter cognitive and functional outcomes in patients with dementia?. Jounal of Family Practice Vol. 46, issue 1:20.
Thuro H. *Beilage für Nervenzerzte*. Munich: Springer, 1997.

Mancini 1993 ***{published data only}***
* Mancini M, Agozzino B, Bompani R. Clinical and therapeutic effects of Ginkgo biloba extract (Egb) compared to placebo in the treatment of patients affected by senile psychorganic dementia on an arteriosclerotic basic [Effecti clinico–terapeutici dell'estratto di Ginkgo biloba (Egb) in confronto a placebo, affetti da demenza psicorganica senile su base arteriosclerotica]. *Gazzetta Medica Italiana - Archivio per le Scienze Mediche* 1993;**152**(3):69–80.

Maurer 1997 ***{published data only}***
* Maurer K, Ihl R, Dierks T, Frolich L. Clinical efficacy of Ginkgo biloba special extract EGb 761 in dementia of the Alzheimer type. *J Psychiatr Res* 1997;**31**(6):645–55.

Oswald 1997 ***{published data only}***
* Oswald WD, Horr R, Oswald B, Steger W, Sappa J. Increase of fluid cognitive factors with Ginkgo biloba special extract EGb 761(R) in elderly patients with mild to moderate organic brain syndrome [Zur Verbesserung fluider, kognitiver Leistungen mit Ginkgo–biloba–Spezialextrakt EGb 761(R) bei Patienten mit leichten bis mittelschweren Hirnleistungsstoerungen im Alter]. *Zeitschrift-Fuer-Gerontopsychologie-und-Psychiatrie* 1997;**10**(3):133–46.

Pidoux 1983 ***{published data only}***
Pidoux B, Bastien C, Niddam S. Clinical and quantitative EEG double-blind study of Ginkgo biloba extract (GBE). *J Cerebral Blood Flow and Metabolism* 1983;**3**(Suppl 1): S556–7.

Rai 1991 ***{published data only}***
* Rai GS, Shovlin C, Wesnes KA. A double-blind, placebo controlled study of Ginkgo biloba extract ('Tanakan') in elderly out-patients with mild to moderate memory impairment. *Current Medical Research and Opinion* 1991; **12**(6):350–355.

Schmidt 1991 ***{published data only}***
Schmidt U, Rabinovici K, Lande S. Einfluss eines Ginkgo-Spezial-extraktes auf die Befindlichkeit bei zerebraler Insuffizienz [Effect of a Ginkgo biloba Special Extract on well–being in cerebral insufficiency]. *Munch. Med. Wochenschr* 1991;**133**(Suppl 1):S15–S18.

Taillandier 1986 *{published data only}*

* Taillandier J, Ammar A, Rabourdin JP, Ribeyre JP, Pichon J, Niddam S, Pierart H. Treatment of cerebral aging disorders with Ginkgo biloba extract. A longitudinal multicenter double-blind drug vs. placebo study [Traitement des troubles du vieillissement cerebral par l'extrait de Ginkgo biloba. Etude longitudinale multicentrique a double insu face au placebo]. *Presse Med* 1986;**15**(31):1583–7.

Van Dongen 2000 *{published data only}*

van Dongen MCJM. *Efficacy of Ginkgo biloba in dementia and cognitive decline. PhD thesis*. Department of Epidemiology, Maastricht University, 1999.
van Dongen MCJM, van Rossum E, Kessels AGH, Sielhorst HJG, Knipschild PG. The efficacy of ginkgo for elderly people with dementia and age-associated memory impairment: new results of a randomized clinical trial. *J American Geriatrics Society* 2000;**48**:1183–94.

Vesper 1994 *{published data only}*

Vesper J, Hansgen K-D. Efficacy of Ginkgo biloba in 90 outpatients with cerebral insufficiency caused by old age. Results of a placebo-controlled double-blind trial. *Phytomedicine* 1994;**1**:9–16.

Vorberg 1989 *{published data only}*

Vorberg G, Schenk N, Schmidt U. Wirksamkeit eines neuen Ginkgo-biloba-Extraktes bei 100 Patienten mit zerebraler Insuffizienz. *Herz + Gefässe* 1989;**9**(7):396–401.

Weitbrecht 1985 *{published data only}*

* Weitbrecht von W-U, Jansen W. Primary degenerative dementia: therapy with Ginkgo biloba extract. Placebo-controlled double-blind and comparative study [Primar degenerative Demenz: Therapie mit Ginkgo–biloba–Extrakt. Plazebo–kontrollierte Doppelblind– und Vergleichsstudie]. *Fortschr Med* 1986;**104**(9):199–202.
Weitbrecht WV, Jansen W. Doubleblind and comparative (Ginkgo biloba versus placebo) therapeutic study in geriatric patients with primary degenerative dementia - a preliminary evaluation. In: Agnoli A, Rapin JR, Scapagnini V, Weitbrecht WV editor(s). *Effects of Ginkgo Biloba Extract on Organic Cerebral Impairment*. Montrouge: John Libby Eurotext Ltd, 1985:91–99.

Wesnes 1987 *{published data only}*

* Wesnes K, Simmons D, Rook M, Simpson P. A double-blind placebo-controlled trial of Tanakan in the treatment of idiopathic cognitive impairment in the elderly. *Human-Psychopharmacology-Clinical-and-Experimental* 1987;**2**(3):159–69.

Winther 1998 *{published data only}*

* Winther K, Randlov C, Rein E, Mehlsen J. Effects of Ginkgo biloba extract on cognitive function and blood pressure in elderly subjects. *Current-Therapeutic-Research* 1998;**59**(12):881–8.

References to studies excluded from this review

Erdincler 1996

* Erdincler DS, Karakoc Y, Toplan S, Onen S, Sukyasyan A, Beger T, Demiroglu C. The effect of Ginkgo biloba glycoside on the blood viscosity and erythrocyte deformability. *Clinical Hemorheology* 1996;**16**(3):271–6.

Franco 1991

Franco L CGNF. Etude multicentrique de l'efficacite de l'extrait de Ginkgo Biloba (EGB 761) dans le traitement des troubles mnesiques lies a l'age. *La Revue De Geriatrie* 1991;**16**:191–5.

Gerhardt 1990

* Gerhardt von G, Rogalla K, Jaeger J. Drug therapy of disorders of cerebral performance. Randomized comparative study of dihydroergotoxine and Ginkgo biloba extract [Medikamentose Therapie von Hirnleistungsstorungen. Randomisierte Vergleichsstudie mit Dihydroergotoxin und Ginkgo–biloba–Extrakt]. *Fortschr Med* 1990;**108**(19):384–8.

Gessner 1985

Gessner B VAKM. Study of the long term action of a Ginkgo Biloba extract on vigilance and mental performance as determined by means of quantitative pharmaco-EEG and psychometric measurements. *Arzneim. Forsch./Drug Res* 1985;**35**:1459–65.

Gomez 1997

Gomez GA. Multicenter study with standardized extract of Ginkgo -Biloba EGB 761 in the treatment of memory alteration, vertigo and tinnitus [Estudio multicentrico del extracto estandardizado de Ginkgo biloba en el tratamiento de los trastornos de la memoria, vertigo y tinnitus]. *Invest Med Int* 1997;**24**(2):31–9.

Haan 1982

Haan J RUWFSGME. Ginkgo-Biloba-Flavonglykoside. Therapiemoeglichkeit der zerebraler Insufficienz. *Med. Welt* 1982;**33**:1001–5.

Hindmarch

Israel 1977

Israël L, Ohlman T, Delomier Y, Hugonot R. Étude psychométrique de l'activité d'un extrait végétal au cours des états d'involution sénile. *Lyon Mediterranee Medical* 1977;**13**(16):1197–9.

Itil 1995

Itil T, Martorano D. Natural substances in psychiatry (Ginkgo biloba in dementia). *Psychopharmacol Bull* 1995;**31**(1):147–58.

Itil 1998

* Itil TM, Erapl E, Ahmed I, Kunitz A, Itil KZ. The pharmacological effects of ginkgo biloba, a plant extract, on the brain of dementia patients in comparison with tacrine. *Psychopharmacol Bull* 1998;**34**(3):391–7.

Koltringer 1995

* Koltringer P, Langsteger W, Eber O. Dose-dependent hemorheological effects and microcirculatory modifications following intravenous administration of Ginkgo biloba special extract EGb 761. *CLIN-HEMORHEOL* 1995;**15**(4):649–656.

Moreau 1975

Moreau P. Un nouveau stimulant circulatoire cerebral. *La Nouvelle Presse Medicale* 1975;**4**:2401–2.

Rigney 1999
* Rigney U, Kimber S, Hindmarch I. The effects of acute doses of standardized Ginkgo biloba extract on memory and psychomotor performance in volunteers. *Phytother Res* 1999;**13**(5):408–15.

Schulz 1991
* Schulz H, Jobert M, Breuel H-P. [Wirkung von Spezialextrakt LI1370 auf das EEG älterer Patienten im Schlafentzugsmodell]. *Münch. Med. Wochenschr* 1991;**133** (Suppl 1):S26–S29.

Semlitsck 1995
* Semlitsch HV, Anderer P, Saletu B, Binder GA, Decker KA. Cognitive psychophysiology in nootropic drug research: effects of Ginkgo biloba on event-related potentials (P300) in age-associated memory impairment. *Pharmacopsychiatry* 1995;**28**(4):134–42.

Teigeler 1984
Teigeler R PL. Ginkgo Biloba bei zerebraler Insuffizienz. *Artzliche Praxis* 1984;**36**:1374.

Vorberg 1985
* Vorberg G. Ginkgo Biloba Extract (GBE) - A long-term Study of chronic cerebral insufficiency in geriatric patients. *Clinical Trials Journal* 1985;**22**:149–57.

Wesnes 1997
* Wesnes KA, Faleni RA, Hefting NR, Hoogsteen G, Houben JJG, Jenkins E, Jonkman JHG, Leonard J, Petrini O, Lier JJ van. The cognitive, subjective, and physical effects of a ginkgo biloba/panax ginseng combination in healthy volunteers with neurasthenic complaints. *Psychopharmacol Bull* 1997;**33**(4):677–83.

Additional references

Beck 1974
Beck AT, Beamesderfer A. Assessment of depression: the depression inventory. In: Pichot P editor(s). *Psychological Measurements in Psychopharmacology. Mod Probl Pharmacopsychiatry 7*. Basel: Karcher, 1974:151–169.

Benton 1974
Benton AL. *Revised visual retention test*. 4th Edition. New York: Psychological Corporation, 1974.

Burke 1991
Burke WJ, Roccaforte WH, Wengel SP. The short form of the Geriatric Depression scale: A comparison with the 30-item form. *J Geriatric Psychiatry Neurol* 1991;**4**:173–178.

Chang 1997
Chang JY, Chang MN. Medicinal uses of Ginkgo biloba. *TODAY'S-THER-TRENDS: Today's-Therapeutic-Trends* 1997;**15**(1):63–74.

Cohen 1988
Cohen RJ, Montaque P, Nathson LS, Swerdlik ME. *Psychological Testing. An introduction to Tests & Measurement*. Mountain Vieuw, California: Mayfield Publishing Company, 1988.

Curtis 1999
Curtis-Prior P, Vere D, Fray P. Therapeutic value of Ginkgo biloba in reducing symptoms of decline in mental function. *J Pharm Pharmacol* 1999;**51**(5):535–41.

De Feudis 1998
De Feudis F. *Ginkgo biloba extract (EGb 761): from chemistry to the clinic*. Weisbaden, Germany: Ullstein Med, 1998.

Ernst 1999
Ernst E, Pittler MH. Ginkgo biliba for dementia A systematic review of double-blind, placebo controlled trials. *Clin Drug Invest* 1999;**17**(4):301–8.

Folstein 1975
Folstein MF, Folstein DE, McHugh PR. Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. *J Psychiat Res* 1975;**12**:189–198.

Guy 1976
Guy W. Clinical Global assessment Scale (CGI). In: Guy W editor(s). *ECDEU Assessment Manual for Psychopharmacology*. Rockville Md: US Dept of Health Education and Welfare, National Institute of Mental Health, 1976:218–222.

Hopfenmüller 1994
Hopfenmüller W. Evidence for a therapeutic effect of Ginkgo biloba special extract. Meta-analysis of 11 clinical studies in patients with cerebrovascular insufficiency in old age [Nachweis der therapeutischen Wirksamkeit eines Ginkgo biloba–Spezialextraktes. Meta–Analyse von 11 klinischen Studien bei Patienten mit Hirnleistungsstörungen im Alter]. *Arzneimittelforschung* 1994;**44**(9):1005–13.

Kleijnen 1992
Kleijnen J, Knipschild P. Ginkgo biloba for cerebral insufficiency. *Br J Clin Pharmacol* 1992;**34**(4):352–8.

Knipschild 1994
Knipschild P, van Dongen M, van Rossum E, Kleijnen J. Clinical experience with ginkgo in patients with cerebral insufficiency. *Rev Bras Neurol* 1994;**30**(Suppl 1):18S–25S.

Massey 1999
Massey AJ. Effectiveness of ginkgo biloba in memory disorders. *J-PHARM-PRACT: Journal-of-Pharmacy-Practice* 1999;**12**(3):217–24.

McKhann 1984
McKhann G, Drachman D Folstein M, et al.Clinical diagnosis of Alzheimer's disease: report fo the NINDCS-ARDRA Work Group under the auspices of the Department of Health and Human Sciences Task Force on Alzheimer's Disease. *Neurology* 1984;**34**:939–44.

Oken 1998
Oken BS, Storzbach DM, Kaye JA. The efficacy of Ginkgo biloba on cognitive function in Alzheimer disease. *Arch Neurol* 1998;**55**(11):1409–15.

Oswald 995
Oswald WD, Fleischmann UM. *Nürnberger Alters Inventar (NAI). NAI-Testmanual und Textband*. 3rd Edition. Gottingen: Hogrefe, 1995.

Overall 1992
Overall JE, Schaltenbrand R. The SKT neuropsychological test battery. *J Geriatric Psychiatry Neurol* 1992;**5**:220–227.

Reisberg 1982
Reisberg B, Ferris SH, De Leon MJ, Crook T. the global deterioration sclae for assessment of primary degenerative dementia. *Am J Psychiatry* 1982;**139**:1136–1139.

Robinson 1964
Robinson RA. The diagnosis and prognosis of dementia. In: Anderson WE editor(s). *Current Achievements in Geriatrics*. London: Cassell, 1964:190–203.

Rosenblatt 1997
Rosenblatt M, Mindel J. Spontaneous hyphema associated with ingestin of Ginkgo biloba extract. *New England Journal of Medicine* 1997;**336**:1108.

Rowin 1996
Rowin J, Lewis SL. Spontaneous bilateral subdural hematomas associated with chronic Ginkgo biloba ingestion. *Neurology* 1996;**46**:1775–7.

Schwartz 1983
Schwartz GE. Development and validation of the Geriatric Evaluation of Relative's rating Instrument (GERRI). *Psychol Rep* 1983;**53**:479–88.

Shader 1974
Shader RI, Harmatz JS, Salzman C. A new scale for clinical assessment in geriatric populations: Sandoz Clinical Assessment-Geriatric (SCAG). *J Am Ger Soc* 1974;**22**: 107–113.

Søholm B 1998
Søholm B. Clinical improvement of memory and other cognitive functions by Ginkgo biloba: Review of relevant literature. *Advances in Therapy* 1998;**15**(1):54–65.

van Dongen 2000
Van Dongen MCJM van Rossum E, Knipschild P. Efficacy of Ginkgo biloba special extracts - Evidence from randomized clinical trials. In: van Beek TA editor(s). *Ginkgo biloba*. Amsterdam: Harwood Academic, 2000.

Warburton 1986
Warburton 1986. Clinical psychopharmacology of Ginkgo biloba extract [Psycho–pharmacologie clinique de l'extrait de Ginkgo biloba]. *La Presse Médicale* 1986;**15**(3): 1595–1604.

Wechsler 1945
Wechsler D. A standardized memory scale for clinical use. *Journal of Psychology* 1945;**19**:87–95.

Yesavage 1982
Yesavage JA, Brink TL, Rose TL, et al.Development and validation of a geriatric deprssion screening scale: A preliminary report. *J Psychiatr Res* 1982;**17**:37–49.

* *Indicates the major publication for the study*

FEEDBACK

Publication date

Summary

The comment was the following query: When can we expect the publication of the review: Ginkgo biloba for dementia and cognitive impairment, which was announced for the 3rd issue 2001?

Author's reply

The review was first published in issue 4/2002

Contributors

Comment: Andreas von Maxen (a.maxen@klinpharm-bremen.de)
Reply: Dymphna Hermans (Coordinator)

SOURCES OF SUPPORT

External sources of support

- Alzheimer Society UK

Internal sources of support

- The University of Oxford UK

NOTES

To make the complex information from the trials available in a more easily accessible form, we have created two additional tables: one which describes the included studies in more detail and a second describing the rating scales used in the trials. It is important that these tables should be read with the review.

INDEX TERMS

Medical Subject Headings (MeSH)

Cognition Disorders [*drug therapy]; Dementia [*drug therapy]; *Ginkgo biloba; *Phytotherapy; Randomized Controlled Trials

MeSH check words

Humans