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Hilton MP, Zimmermann EF, Hunt WT

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TABLE OF CONTENTS

[Intervention Review]

Ginkgo biloba for tinnitus

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ABSTRACT

Background

This is an update of a Cochrane review first published in *The Cochrane Library* in Issue 2, 2004 and previously updated in 2007 and 2009.

Tinnitus can be described as the perception of sound in the absence of external acoustic stimulation. At present no specific therapy for tinnitus is acknowledged to be satisfactory in all patients. There are a number of reports in the literature suggesting that Ginkgo biloba may be effective in the management of tinnitus. However, there also appears to be a strong placebo effect in tinnitus management.

Objectives

To assess the effect of Ginkgo biloba in patients who are troubled by tinnitus.

Search methods

We searched the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL); PubMed; EMBASE; AMED; Web of Science; BIOSIS Previews; Cambridge Scientific Abstracts; ICTRP and additional sources for published and unpublished trials. The date of the most recent search was 12 March 2012.

Selection criteria

Adults (18 years and over) complaining of tinnitus or adults with a primary complaint of cerebral insufficiency, where tinnitus forms part of the syndrome.

Data collection and analysis

Both original authors independently extracted data and assessed trials for quality. For the 2012 update two authors determined trial eligibility, extracted data, analysed data and updated the contents of the review.

Main results

Four trials with a total of 1543 participants were included in the review; we assessed all the included studies as having a low risk of bias. Three trials (1143 participants) included patients with a primary complaint of tinnitus and one (400 participants) included patients with mild to moderate dementia, some of whom had tinnitus.

There was no evidence that Gingko biloba was effective in patients with a primary complaint of tinnitus. In the study of patients with dementia, mean baseline levels of tinnitus were low (1.7 to 2.5 on a 10-point subjective symptom rating scale). A small but statistically significant reduction of 1.5 and 0.7 points was seen in patients taking Gingko biloba with vascular dementia and Alzheimer's disease respectively. The practical clinical significance of this is unclear. The incidence of side effects was low.

Authors' conclusions

The limited evidence does not demonstrate that Ginkgo biloba is effective for tinnitus when this is the primary complaint.

PLAIN LANGUAGE SUMMARY

Ginkgo biloba for tinnitus

People with tinnitus hear sounds such as crackling or whistling in the absence of external noise. Noises appear to arise in the ears or inside the head and may be experienced all of the time, or only intermittently. The causes of tinnitus are not yet fully understood and a variety of treatments are offered including medication, psychotherapy, noise 'maskers' and tinnitus retraining therapy. The review of trials assessed the effectiveness of extract of Ginkgo biloba. Few good-quality trials were found. Four studies were included in the review, with a total of 1543 participants. The included studies were overall at low risk of bias. There was no evidence that Ginkgo biloba is effective for tinnitus when this is the primary complaint.

BACKGROUND

This is an update of a Cochrane review first published in *The Cochrane Library* in Issue 2, 2004 and previously updated in 2007 and 2009. It is one of a number of tinnitus reviews produced by the Cochrane Ear, Nose and Throat Disorders Group, which use a standard Background. The following paragraphs (Description of the condition) are based on earlier work in the following reviews and reproduced with permission: Baldo 2012; Bennett 2012; Hilton 2004; Hobson 2012; Phillips 2010.

Description of the condition

Tinnitus can be described as the perception of sound in the absence of external acoustic stimulation. For the patient it may be trivial or it may be a debilitating condition (Luxon 1993). The quality of the perceived sound can vary enormously from simple sounds such as whistling or humming to complex sounds such as music. The patient may hear a single sound or multiple sounds. Tinnitus may be perceived in one or both ears, within the head or outside the body. The symptom may be continuous or intermittent. Tinnitus is described in most cases as subjective - meaning that it cannot be heard by anyone other than the patient. While, for the patient, this perception of noise is very real, because there is no corresponding external sound it can be considered a phantom, or false, perception. Objective tinnitus is a form of tinnitus which can be detected by an examiner, either unaided or using a listening aid such as a stethoscope or microphone in the ear canal. This is much less common and usually has a definable cause such as sound generated by blood flow in or around the ear or unusual activity of the tiny muscles within the middle ear. Tinnitus may be associated with normal hearing or any degree of hearing loss and can occur at any age.

It is important to distinguish between clinically significant and non-significant tinnitus (Davis 2000) and several different classifications have been proposed (Dauman 1992; McCombe 2001; Stephens 1991). Dauman, for example, makes a distinction between 'normal' (lasting less than five minutes, occurring less than once a week and experienced by most people) and 'pathological' tinnitus (lasting more than five minutes, occurring more than once a week and usually experienced by people with hearing loss).

Aetiology

Almost any form of disorder involving the outer, middle or inner ear or the auditory nerve may be associated with tinnitus (Brummett 1980; Shea 1981). However, it is possible to have severe tinnitus with no evidence of any aural pathology. Conversely, tinnitus can even exist without a peripheral auditory system: unilateral tinnitus is a common presenting symptom of vestibular schwannomas (acoustic neuromas), which are rare benign tumours of the vestibulo-cochlear nerve. When these neuromas are removed by a translabyrinthine route, the cochlear nerve can be severed. Despite the effective removal of their peripheral auditory mechanisms, 60% of these patients retain their tinnitus postoperatively (Baguley 1992). This suggests the fundamental importance of the central auditory pathways in the maintenance of the symptom, irrespective of trigger.

Many environmental factors can also cause tinnitus. The most relevant and frequently reported are:

- acute acoustic trauma (for example, explosions or gunfire) (Christiansson 1993; Chung 1980; Melinek 1976; Mrena 2002; Temmel 1999);
- airbag inflation (Saunders 1998); toy pistols (Fleischer 1999);
- exposure to occupational noise; 'urban noise pollution' (Alberti 1987; Axelsson 1985; Chouard 2001; Daniell 1998; Griest 1998; Kowalska 2001; McShane 1988; Neuberger 1992; Phoon 1993); and
- exposure to recreational and amplified music (Becher 1996; Chouard 2001; Lee 1999; Metternich 1999).

Pathophysiology

Over 50 years ago, Heller and Bergman demonstrated that if 'normal' people (with no known cochlear disease) were placed in a quiet enough environment, the vast majority of them would experience sounds inside their head. They concluded that tinnitus-like activity is a natural phenomenon perceived by many in a quiet enough environment (Heller 1953).

Mazurek has shown that pathologic changes in the cochlear neurotransmission, e.g. as a result of intensive noise exposure or ototoxic drugs, can be a factor in the development of tinnitus (Mazurek 2007).

In the 'neurophysiological model' of tinnitus (Jastreboff 1990; Jastreboff 2004) it is proposed that tinnitus results from the abnormal processing of a signal generated in the auditory system. This abnormal processing occurs before the signal is perceived centrally. This may result in 'feedback', whereby the annoyance created by the tinnitus causes the individual to focus increasingly on the noise, which in turn exacerbates the annoyance and so a 'vicious cycle' develops. In this model tinnitus could therefore result from continuous firing of cochlear fibres to the brain, from hyperactivity of cochlear hair cells or from permanent damage to these cells being translated neuronally into a 'phantom' sound-like signal that the brain 'believes' it is hearing. For this reason tinnitus may be compared to chronic pain of central origin - a sort of 'auditory pain' (Briner 1995; Sullivan 1994).

The relationship between the symptom of tinnitus and the activity of the prefrontal cortex and limbic system has been emphasised. The limbic system mediates emotions. It can be of great importance in understanding why the sensation of tinnitus is in many cases so distressing for the patient. It also suggests why, when symptoms are severe, tinnitus can be associated with major depression, anxiety and other psychosomatic and/or psychological disturbances, leading to a progressive deterioration of quality of life (Lockwood 1999; Sullivan 1989; Sullivan 1992; Sullivan 1993).

Prevalence

Epidemiological data reports are few. The largest single study was undertaken in the UK by the Medical Research Council Institute of Hearing Research and was published in 2000 (Davis 2000). This longitudinal study of hearing questioned 48,313 people; 10.1% described tinnitus arising spontaneously and lasting for five or more minutes at a time and 5% described it as moderately or severely annoying. However, only 0.5% reported tinnitus having a severe effect on their life. This is another of the paradoxes of tinnitus: the symptom is very common but the majority of people who experience it are not particularly concerned by it. These figures from the UK are broadly consistent with data collected

by the American Tinnitus Association (ATA) which suggest that tinnitus may be experienced by around 50 million Americans, or 17% of the US population (ATA 2004). Data also exist for Japan, Europe and Australia (Sindhusake 2003), and estimates suggest that tinnitus affects a similar percentage of these populations, with 1% to 2% experiencing debilitating tinnitus (Seidman 1998). The Oregon Tinnitus Data Archive (Oregon 1995) contains data on the characteristics of tinnitus drawn from a sample of 1630 tinnitus patients. The age groups with the greater prevalence are those between 40 and 49 years (23.9%) and between 50 and 59 years (25.6%).

Olszewski showed in his study that the risk of tinnitus increases in patients over 55 years old who suffer from metabolic conditions and cervical spondylosis (Olszewski 2008).

Diagnosis

Firstly a patient with tinnitus may undergo a basic clinical assessment. This will include the relevant otological, general and family history, and an examination focusing on the ears, teeth and neck and scalp musculature. Referral to a specialist is likely to involve a variety of other investigations including audiological tests and radiology. Persistent, unilateral tinnitus may be due to a specific disorder of the auditory pathway and imaging of the cerebellopontine angle is important to exclude, for example, a vestibular schwannoma (acoustic neuroma) - a rare benign tumour of the cochleo-vestibular nerve. Other lesions, such as glomus tumours, meningiomas, adenomas, vascular lesions or neuro-vascular conflicts, may also be detected by imaging (Marx 1999; Weissman 2000).

Treatment

At present no specific therapy for tinnitus is acknowledged to be satisfactory in all patients. Many patients who complain of tinnitus, and also have a significant hearing impairment, will benefit from a hearing aid. Not only will this help their hearing disability but the severity of their tinnitus may be reduced.

A wide range of therapies have been proposed for the treatment of tinnitus symptoms. Pharmacological interventions used include cortisone (Koester 2004), vasodilators, benzodiazepines, lidocaine and spasmolytic drugs. The use of anticonvulsants in treating tinnitus was found to be ineffective in a Cochrane review, and 18% of patients experienced side effects (Hoekstra 2011). Antidepressants are commonly prescribed for tinnitus. However, two reviews (Baldo 2012; Robinson 2007) showed that there is no indication that tricyclic antidepressants have a beneficial effect.

Hyperbaric oxygen therapy (HBOT) can improve oxygen supply to the inner ear which, it is suggested, may result in an improvement in tinnitus, however a Cochrane review found insufficient evidence to support this (Bennett 2012).

Studies have been carried out into the effect of cognitive behavioural therapy (CBT) on tinnitus (Andersson 1999). Another Cochrane review has shown that CBT can have an effect on the qualitative aspects of tinnitus and can improve patients' ability to manage the condition (Martinez-Devesa 2010).

Other options for the management of patients with tinnitus include transcranial magnetic stimulation (Meng 2011), tinnitus masking (use of 'white noise' generators) (Hobson 2012), music therapy (Argstatter 2008), reflexology, hypnotherapy and traditional Chinese medicine (TCM), including acupuncture (Li 2009).

Description of the intervention

Ginkgo biloba

Extracts of Ginkgo biloba leaves have been used for medicinal purposes for at least 5000 years in China, where they form an important component of the traditional Chinese pharmacopoeia (a book which lists drugs and instructions for their use). More recently the extracts have been used in Western countries. In several countries, including the USA, Canada and the UK the extracts are widely available in the form of non-prescription food supplements. In parts of Europe, particularly France and Germany, the extract is registered as a drug and is consistently one of the most commonly prescribed medications.

There are several components in the available preparations. A purified and enriched liquid extract is prepared from dried leaves of the maidenhair plant. The liquid extract is dried to give one part extract from 50 raw leaves. The most important active chemical compounds fall into two categories: flavonoids (ginkgo-flavone glycosides) and terpenoids (ginkgolides A, B, C, J and bilobalide). Ginkgolides appear to be unique to Ginkgo biloba and have not been isolated from any other plant species. There are several commercially available preparations but the four that have been used in most trials of Ginkgo biloba contain standardised amounts of these substances. EGb761 (Tebonin®, Tanakan®, Rökan®) contains 24% ginkgo-flavone glycosides and 6% terpenoids. LI 1370 (Kaveri®) contains 25% ginkgo-flavone glycosides and 6% terpenoids (Blumenthal 1998). Although the quantities are standardised the manufacturing process is different and the ratio of active ingredients within each sub-class may be different. There is no standardisation for food supplement preparations.

Several mechanisms of action of Ginkgo have been proposed in the light of the many active ingredients. Human, animal and in vitro studies (Kleijnen 1992) have suggested the following effects:

1. A vasoregulatory effect (altering the tone of blood vessels) promoting increased blood flow. A double-blind randomised trial (Koltringer 1989) in 30 patients of 200 mg EGb 761 daily for four days showed increased skin perfusion (greater blood flow) with reduced blood viscosity and elasticity compared to control. Another small randomised trial demonstrated increased nail-fold capillary blood flow and decreased erythrocyte (red blood cell) aggregation (Jung 1990).
2. Antagonism of platelet activating factor (PAF). This effect is specific to the ginkgolides (predominantly B). PAF causes platelet (a blood constituent involved in blood clot formation) aggregation, neutrophil degranulation (activation of immune cells within the blood stream) and oxygen radical production. Ginkgolides appear to protect against the effects of hypoxic brain injury from cerebral ischaemia (permanent brain damage caused by insufficient blood and oxygen supply) in laboratory animals (Braquet 1991; DeFeudis 1991a).
3. Changes in neuron (nerve cell) metabolism in animal studies (DeFeudis 1991b). In elderly patients with cerebral insufficiency (see definition below) beneficial EEG (an electroencephalogram which measures patterns of the brain's electrical activity)

changes have been reported (Hofferberth 1989; Hofferberth 1991).

4. Prevention of cell membrane damage by free radicals. Ginkgo extracts have free radical scavenging properties as demonstrated by in vitro studies (Pincemail 1989).

Ginkgo has been most widely prescribed as a treatment for peripheral vascular disease (insufficient blood flow to the limbs because of damage to blood vessels) and cerebral insufficiency. Cerebral insufficiency is difficult to define precisely but conventionally refers to a syndrome including one or more of: concentration difficulties; loss of memory; confusion; lack of energy; tiredness; reduced physical performance; depressive mood; anxiety; dizziness; headache; tinnitus and absent mindedness. Experimental evidence for its effects on cognitive functions in various forms of dementia are presented by several authors (Hopfenmuller 1994; Kleijnen 1992; Knipschild 1994; Oken 1998; Soholm 1998).

The most commonly reported side effect of Ginkgo biloba is mild gastrointestinal disturbance (e.g. stomach pains, change in bowel habit). Serious side effects are rare, but include bleeding problems, interaction with anticoagulant medication and seizures (Ernst 2002).

There are a number of reports in the literature suggesting that Ginkgo biloba may be effective in the management of tinnitus (Artieres 1978; Coles 1988; Gananca 1986; Sprenger 1986; Ziegler 1969). A previous systematic review identified only a small number of randomised controlled trials, most of which were of low methodological quality. Only one trial appeared methodologically sound, and reported a small effect of Ginkgo biloba in reducing the perceived loudness of tinnitus (Ernst 1999). However, there also appears to be a strong placebo effect in tinnitus management. Duckert et al (Duckert 1984) demonstrated the importance of this. They performed an initial double-blind randomised trial of the effects of lignocaine (a local anaesthetic) on tinnitus sufferers; 25% of patients in the control group reported a significant change in their tinnitus. However, following completion of the trial the 25 patients who had received the 'placebo' injection of saline (salty water) were contacted and offered the 'real' treatment, although once again received only a saline injection. Of the 20 patients who received this second injection eight (40%) reported a change of greater than 25% in their tinnitus severity (six patients improved, two deteriorated).

OBJECTIVES

To assess the effect of Ginkgo biloba in patients who are troubled by tinnitus.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials.

Types of participants

Adults (18 years and over) complaining of tinnitus.

We included trials which considered Ginkgo biloba in patients who presented with other primary complaints, but in whom tinnitus was reported as an outcome variable. The characteristics of patients in this group may be different to patients whose principal complaint is tinnitus: it is likely that this included patients who did not consider their tinnitus to be intrusive or irritating and it is not clear that the results in this subgroup necessarily translate to patients who are distressed by their tinnitus and actively seek medical help or intervention. Therefore, tinnitus as a primary versus secondary reported complaint was a key stratification variable for the review.

We excluded patients with tinnitus that was associated with a conductive hearing loss (hearing loss due to inadequate transmission of sound to the inner ear), intracranial vascular malformation (blood vessel abnormality within the brain), or palatal myoclonus (repetitive twitching movement of the palate) from the review.

Types of interventions

Ginkgo biloba versus placebo.

There is no 'gold standard' treatment for tinnitus that can act as a satisfactory reference active treatment.

Since there is a significant psychological component present by the time patients have distressing tinnitus, the placebo effect of treatment is of special relevance and we do not believe that an experimental comparison of Ginkgo against untreated patients can clarify specific versus non-specific effects of treatment.

Most reported trials of Ginkgo biloba treatment use dosages in the range 120 to 200 mg daily. All trials were considered for inclusion in this review, irrespective of dosage used. However, sensitivity analysis was planned to consider the bias that may occur if trials were included that report results with dosages falling outside of this purported therapeutic window.

Types of outcome measures

1) Patients' subjective assessment of tinnitus before, during and after treatment.

- Change in loudness of tinnitus.
- Change in overall severity of tinnitus, its impact on quality of life or both.

There are a number of validated questionnaires which provide a scale of severity of disability and handicap associated with tinnitus (e.g. the 'Tinnitus Handicap Inventory' (Newman 1996) and the 'Tinnitus Questionnaire' (Hallam 1988)). Whilst the use of such validated and relatively robust assessment tools is preferable, we considered any categorical distinction between different grades of loudness and 'severity'.

2) Change in psychoacoustic parameters associated with tinnitus before, during and after treatment.

- Tinnitus masking thresholds with formal audiometry.

There is ample evidence to show that there is no overall correlation between loudness of tinnitus (as judged by masking threshold) and the degree of distress or disability. However, this applies to a population comparison. When considering the potential for benefit in any one individual, it seems reasonable to consider that an intervention which reduces perceived loudness may be a useful adjunctive measure for a patient undergoing cognitive or

behavioural therapy. We therefore considered a change in loudness as judged by masking thresholds as a secondary outcome measure.

- Change in thresholds on pure-tone audiometry.

3) Side effects and adverse effects of treatment.

Search methods for identification of studies

We conducted systematic searches for randomised controlled trials. There were no language, publication year or publication status restrictions. The date of the last search was 12 March 2012, following previous searches in 2009, 2007 and 2004.

Electronic searches

We searched the following databases from their inception: the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 2); PubMed; EMBASE; AMED; CINAHL; LILACS; KoreaMed; IndMed; PakMediNet; CAB Abstracts; Web of Science; BIOSIS Previews; ISRCTN; ClinicalTrials.gov; ICTRP; Google Scholar and Google.

We modelled subject strategies for databases on the search strategy designed for CENTRAL. Where appropriate, we combined subject strategies with adaptations of the highly sensitive search strategy designed by the Cochrane Collaboration for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 Box 6.4.b. (Handbook 2011)). Search strategies for the major databases including CENTRAL are provided in Appendix 1.

Searching other resources

We scanned reference lists of identified studies for further trials. We searched PubMed, TRIPdatabase, *The Cochrane Library* and Google to retrieve existing systematic reviews possibly relevant to this systematic review, in order to search their reference lists for additional trials. We sought abstracts from conference proceedings via the Cochrane Ear, Nose and Throat Disorders Group Trials Register.

Data collection and analysis

Selection of studies

Two authors independently selected trials for inclusion and extracted the data using standardised forms. Disagreement was resolved by consensus.

Data extraction and management

The authors extracted data independently onto standardised data forms. We included studies that reported incomplete or ambiguous data when the data were obtained by contacting the authors.

Assessment of risk of bias in included studies

In the original versions of this review we assessed the quality of identified studies using a modification of the method of Schulz et al (Schulz 1995).

For the 2012 update, two authors undertook assessment of the risk of bias of the included trials independently, taking the following into consideration, as guided by the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011):

- sequence generation;
- allocation concealment;
- blinding;
- incomplete outcome data;
- selective outcome reporting; and
- other sources of bias.

We used the Cochrane 'Risk of bias' tool in RevMan 5.1 (RevMan 2011), which involved describing each of these domains as reported in the trial and then assigning a judgement about the adequacy of each entry: 'low', 'high' or 'unclear' risk of bias.

Data synthesis

We planned to analyse data on an intention-to-treat basis. In this version of the review we performed no pooling of data to determine outcomes. In future reviews, if more homogenous data are available, we will report standardised mean differences or, in order to determine an odds ratio with a fixed-effect model, we will transform data to a binary outcome.

RESULTS

Description of studies

Results of the search

From the 2012 update searches, we retrieved a total of 43 references, which reduced to 31 once duplicates were removed. Following assessment of the 31 references, we identified one further relevant trial, Napryeyenko 2009, which was a study of Ginkgo biloba in dementia. No trials were considered eligible but then excluded at this update of the review.

From the 2009 update searches, we retrieved a total of 41 references: 29 of these were removed in first-level screening (including five duplicates), leaving 12 references for further consideration. None were relevant to the review.

In 2006, 172 trials were identified by the combined searches and a further 49 from the updated searches for this review. Scrutinising references yielded a further 21 trials. One author scanned the search results to identify 25 trials that appeared broadly to address the subject of the review and we scrutinised the full text of these articles for eligibility. Eleven of these trials were not publications of original controlled trials (one was a pre-notification of a trial starting), leaving 14 trials for consideration.

The quality of trials reported was generally poor. Seven of the trials studied patients whose primary complaint was tinnitus. Seven of the trials studied patients whose primary complaint was cerebral insufficiency in which tinnitus was included as a defining criteria and outcome measure.

As might be expected, the seven trials considering patients with tinnitus alone included more comprehensive outcome criteria and more description relating to the duration and cause of tinnitus. The trial by Novotny (Novotny 1999) included 33 patients with Ménière's disease (from a total of 70 patients) and was not included because of the inherent variability in symptoms in patients with Ménière's disease that could act as a significant confounding factor in a trial with small patient population. With the exception of Napryeyenko 2009, in trials of cerebral insufficiency tinnitus was one of up to 12 symptoms considered to define the syndrome. Tinnitus was not

reported by every patient in each trial. Independent data were not presented (and could not be obtained) on the subgroup of patients who complained of tinnitus at the onset of the trial. The causes of cerebral insufficiency were either not presented or heterogenous in the majority of studies.

Duration and dose of treatment was relatively consistent amongst the trials. Ten of the trials comparing active Ginkgo against placebo used a dose in the range 120 to 160 mg for 12 weeks. There were two cross-over trials in which patients received both active treatment and placebo (Arrigo 1986; Holgers 1994). In two trials (Holgers 1994; Morgenstern 2001) patients were all pre-treated with a two-week course of Ginkgo biloba extract before randomisation into treatment or placebo groups. All trials used standardised preparations of Ginkgo biloba extracts as the experimental drug.

Most trials of patients with cerebral insufficiency and the trial by Novotny 1999 reported only a simple categorical rating of tinnitus, e.g. 'present/absent' or 'none/slight/severe' before, during and after treatment. This subjective, unvalidated reporting is unsatisfactory and there were no useable data available from these trials. In Napryeyenko 2009, tinnitus was assessed on an 11-point scale of severity at baseline and at intervals during the study.

Included studies

Following assessment, we included four studies in the review (Drew 2001; Morgenstern 1997; Napryeyenko 2009; Rejali 2004). See Characteristics of included studies table.

Studies with 'tinnitus' as the primary complaint

Drew 2001 was a double-blind, placebo-controlled trial that recruited 978 participants (676 male, 302 female) into 489 pairs who were matched on the basis of age, sex and duration of tinnitus. The randomisation strategy comprised a computer-generated randomised code. Patients were recruited via adverts in the national press and tinnitus society magazines and enrolled via a postal questionnaire. Their tinnitus had to be stable and of between one and five years duration. No Ginkgo biloba or other tinnitus treatment was permitted in the six months prior to the trial. Participants received placebo or 150 mg of LI 1370 daily for 12 weeks. Several outcome measures were considered. The primary measures were change in tinnitus loudness (six-point categorical scale) and change in troublesome nature (five-point categorical scale). Secondary outcome measures included an overall 'tinnitus severity score' (composite of three subscales for loudness, awareness and impact; total 19 questions) and assessment for confounding factors (variability of tinnitus, cerebral impairment, compliance and side effects).

No audiometric data were recorded. Assessment questionnaires were completed at four weeks, 12 weeks and 14 weeks.

Morgenstern 1997 was a double-blind, placebo-controlled trial that recruited 99 patients with a mean of 4.5 years tinnitus. Patients with objective tinnitus, middle ear disease and systemic illness were excluded. All patients received a two-week initial course of placebo medication and were then randomised to receive 12 weeks of either placebo or 120 mg daily of EGb761 (Tebonin®; Schwabe). Twenty-six of the 99 patients did not complete the trial (14 experimental, 12 control). The primary outcome measure was tinnitus loudness, determined by audiometric masking, in the worst affected ear. These data were analysed on an intention-to-treat basis with the last available audiometric result carried forward to the final analysis. Secondary outcome measures included subjective ratings of tinnitus intensity on a five-point rating scale from nil to severe, and a grading of the patient's impression of the treatment effect on a categorical scale from 'highly ineffective' to 'highly effective'. Only results of the audiometric masking were fully reported in the published article. We contacted Schwabe, the pharmaceutical company which supported the trial, and asked for the raw data. They replied but declined to provide the requested data.

Rejali 2004 was a double-blind, placebo-controlled trial which recruited adult patients from general otolaryngology clinics whose principal or only complaint was tinnitus. Patients with active middle or external ear disease and patients who had previously tried Gingko biloba were excluded. Sixty-six patients were entered into the trial, with 60 (34 men, 26 women) completing part of the study (see below). Patients received 120 mg of Ginkgo biloba for 12 weeks and the control group received placebo tablets also provided by the pharmaceutical company. The primary outcome measures were scores on the Tinnitus Handicap Inventory (THI), Glasgow Health Status Inventory (GSHI) and subjective rating of tinnitus improvement and change in pure-tone audiometry thresholds. Sixty patients completed the questionnaire assessment pre- and post-intervention, but there was a significant attrition rate of patients returning for audiometry and this parameter is not considered in the review.

Studies with 'cerebral insufficiency' as the primary complaint

Napryeyenko 2009 was a double-blind, randomised, multicentre, placebo-controlled trial that recruited 400 adult patients with mild to moderate dementia (218 patients with Alzheimer's dementia and 182 with vascular dementia). Patients received a daily dose of 240 mg Ginkgo biloba or placebo. The primary outcome measure was cognitive (SKT test battery). All patients self rated presence and severity of tinnitus on an 11-point box scale from 'absent' to 'extremely severe'. Assessments were made at baseline, week 12 and week 22.

Excluded studies

We excluded 10 studies (Arrigo 1986; Bruchert 1991; Eckmann 1982; Halama 1988; Halama 1991; Holgers 1994; Meyer 1986; Morgenstern 2001; Novotny 1999; Schmidt 1991; von Wedel 1995). Reasons for exclusion are reported in the Characteristics of excluded studies table.

Risk of bias in included studies

Although the quality of trials identified by the literature searches was generally low, the methodological quality of the four included studies is high and there is a low risk of bias. All trials reported computer-generated randomised sequences with appropriate allocation concealment and blinding of assessors to study group. In only one study were data not reported (and actively withheld) by the authors on an outcome that had been measured as per pre-trial protocol.

Effects of interventions

Effect of Ginkgo biloba on tinnitus as a primary complaint

The largest study, Drew 2001, reported no difference between control and experimental groups at the end of the trial. Of the Ginkgo-treated patients, 13.6% reported an improvement in their

tinnitus, compared to 12.4% of the placebo-treated patients. Further analysis of the data for the matched pairs demonstrated no significant difference in mean scores for tinnitus loudness, awareness or impact between the pairs. Baseline measures of tinnitus variability, cerebral performance and compliance with treatment were comparable between groups.

In Morgenstern 1997 the primary outcome measure of tinnitus loudness, matched by audiometry, demonstrated a small, non-significant improvement in the treatment group of 42.3 (36.6 to 48.1) to 39.0 (31.9 to 46.1) dB, compared to 44.1 (39.0 to 49.2) to 45.1 (39.1 to 51.2) dB in the control group. The limited information presented on subjective outcome measures did not demonstrate a significant difference between the groups.

In Rejali 2004 there was no difference in outcome between control and experimental groups. The mean difference on the Tinnitus Handicap Inventory was -2.2 for the control group versus -4.7 for the experimental group (P = 0.51, confidence interval (CI) -10.5 to 5.1). The mean difference on the Glasgow Health Status Inventory was 2.52 for the control group versus 1.94 for the experimental group (P = 0.78, CI -4.8 to 3.6). The proportion of patients who subjectively reported improvement was 13% in the control group and 8.3% in the experimental group.

Effect of Ginkgo biloba on tinnitus with 'cerebral insufficiency' as a primary complaint

In Napryeyenko 2009 a significant difference in change of subjective tinnitus severity rating was noted at 22 weeks in both groups of dementia patients compared to placebo. In Alzheimer's dementia patients the mean changes in tinnitus scores for the control group versus the experimental group were 0.0 ± 0.8 versus -0.7 ± 1.4 respectively (P < 0.01). In vascular dementia patients the mean differences in tinnitus scores in the control versus the experimental group were 0.0 ± 0.9 versus -1.5 ± 1.8 respectively (P < 0.01). Baseline values in both groups ranged from 1.7 to 2.5 and were not significantly different.

Side effects of treatment

There was no difference in the reporting of side effects of treatment. In Drew 2001, 9.5% of patients receiving placebo and 10.6% of patients receiving Ginkgo biloba reported side effects, of which approximately one-third in each group were gastrointestinal upset. In Rejali 2004, patients reported diarrhoea (6% placebo, 3% experimental) and headache (3% in each group). One patient in a study excluded from this review (Halama 1991) was reported to have an allergic reaction to Ginkgo biloba although no further details of the reaction were provided. In Napryeyenko 2009, 5% of patients receiving EGb761 reported significant adverse events, compared to 8% in the control group. No side effect was significantly more common in the treated group.

DISCUSSION

This systematic review examines the effect of Ginkgo biloba on tinnitus under two circumstances: in patients presenting with tinnitus as a primary complaint and in patients with cerebral insufficiency in whom tinnitus was recorded as both a defining feature of the syndrome and an outcome measure for treatment. All trials were relatively homogeneous with respect to dose of Ginkgo biloba (120 to 150 mg daily) and duration of treatment (typically 6 to 12 weeks). The methodology of most trials was questionable.

The trials of cerebral insufficiency excluded from the review were generally of inadequate methodological quality. In all these trials, tinnitus was included as a symptom of cerebral insufficiency, when clustered with other symptoms such as memory loss, poor concentration, lethargy and depression. The only rating of tinnitus was subjective; in some cases asking the respondent to report only whether there was an improvement from pre-treatment. This is not a robust assessment technique in any trial and must be an additional cause for concern when many of the trial participants complain of memory loss! None of the excluded trials indicated the proportion of patients for whom tinnitus was a complaint (as distinct from a non-intrusive symptom acknowledged only on direct questioning). Not all patients reported tinnitus as one of their symptoms at the outset of the trials, and it is possible that the subgroup of patients reporting tinnitus at the conclusion of the trial included some patients who developed the symptom in the interim. In contrast, the trial of Napryeyenko 2009 included a pre- and post-assessment of severity of tinnitus on an appropriate linear visual analogue scale for all patients included in the trial.

Although the standard of the trials falls well below that which would allow inclusion in the review as evidence of an effect, it is salient to note that the majority of these trials do report an improvement in tinnitus, as is the conclusion of Napryeyenko 2009. However, the results in Napryeyenko 2009 also highlight the distinction of tinnitus as reported by patients with cognitive insufficiency, and patients for whom tinnitus is the primary complaint. Mean scores for tinnitus severity at baseline were approximately 2 out of 10 on a linear scale of severity. It must be considered that the change in tinnitus rating, whilst *statistically* significant, is unlikely to be clinically significant.

The principal interest in the outcome of this review and in other excluded studies is to hypothesise why there might be a favourable response to Ginkgo biloba when tinnitus is associated with cognitive insufficiency:

1. The aetiology of tinnitus in cognitive insufficiency is fundamentally different from primary tinnitus. For example, tinnitus in cognitive insufficiency may be caused by central vascular insufficiency or neural metabolic disorder, whereas in primary tinnitus the initiating pathology is a cochlear disorder. Changes in vascular perfusion and neuronal metabolism are well-documented effects of Ginkgo biloba in animal and human studies (vide supra).
2. Improved cognitive functioning with Ginkgo biloba allows habituation to the tinnitus. Habituation to repetitive presentation of a sensory stimulus or perception is the norm. There is a strong psychological component in appropriate habituation to tinnitus. If Ginkgo biloba causes a significant improvement in overall cognitive functioning then a positive effect on tinnitus may be real, but non-specific. A recent Cochrane review, however, concluded that the evidence that Ginkgo biloba has a predictable and clinically significant benefit for people with dementia or cognitive impairment is inconsistent and unreliable (Birks 2009).

It is not possible to address this question on the basis of the current evidence but it is a key area to consider for future development. It is unlikely that the aetiology of tinnitus is the same for every tinnitus sufferer. Ginkgo has been shown to affect vascular permeability and neuronal metabolism. If a greater level of understanding and

diagnostic accuracy can be reached about the different aetiologies of tinnitus, this may naturally highlight subgroups of tinnitus patients in whom further controlled trials of Ginkgo biloba are worth considering.

AUTHORS' CONCLUSIONS

Implications for practice

The limited evidence from the included studies does not demonstrate that Ginkgo biloba is effective for tinnitus when tinnitus is the primary complaint.

Implications for research

1. Future research should include one of the validated tinnitus handicap questionnaires as an outcome measure before, during and after treatment.
2. Any future research into the effects of Ginkgo biloba on tinnitus must be careful to define its patient population.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Drew 2001

Methods	Randomised, double-blind, placebo-controlled trial
Participants	978 tinnitus sufferers recruited from national press adverts
Interventions	150 mg LI1370 daily versus placebo for 12 weeks
Outcomes	1. Change in tinnitus loudness 2. Change in troublesome nature of tinnitus 3. Tinnitus severity score (composite measure) 4. Variability of tinnitus 5. Symptoms of cognitive impairment 6. Compliance with treatment 7. Side effects
Notes	Recruited as matched pairs Authors contacted for raw data

Risk of bias

Bias	Authors' judgement	Support for judgement

Drew 2001 *(Continued)*

Random sequence generation (selection bias)	Low risk	Participants were paired according to described criteria. Each pair was then allocated 2 numbers from a randomly arranged code. One number corresponded to placebo treatment and one to active treatment.
Allocation concealment (selection bias)	Low risk	See above
Blinding (performance bias and detection bias) All outcomes	Low risk	The study was carried out entirely by mail and telephone. Telephone contact was only to resolve problems or answer enquiries. Data entry and initial analyses were carried out by a researcher blinded to the participant's allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete data for matched pairs were used. Unmatched analyses did not provide any additional information and were therefore not included
Selective reporting (reporting bias)	Low risk	Multiple outcomes, all reported
Other bias	Low risk	—

Morgenstern 1997

Methods	Randomised, double-blind, placebo-controlled trial
Participants	99 tinnitus patients aged over 18 Minimum 2 months duration of tinnitus
Interventions	12 weeks of placebo or 120 mg EGb761 daily
Outcomes	1. Tinnitus loudness measured by audiometric masking in worst ear 2. Rating of tinnitus severity: 5-point scale
Notes	Significant attrition from each group: 14/49 placebo, 12/50 control Authors contacted for raw data

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Adequate
Blinding (performance bias and detection bias) All outcomes	Low risk	—
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Relatively high drop-out rate; equally spread across control and experimental groups

Morgenstern 1997 *(Continued)*

Selective reporting (reporting bias)	High risk	Only data for audiometric masking of tinnitus reported. Tinnitus ratings and patient's view of treatment success were measured but are not in the trial report, and the authors declined to provide the information when contacted
Other bias	Unclear risk	—

Napryeyenko 2009

Methods	Randomised, double-blind, multicentre, placebo-controlled trial
Participants	400 patients aged over 50 with Alzheimer's dementia (n = 218) or vascular dementia (n = 182).
Interventions	22 weeks of placebo or 240 mg EGb761® daily
Outcomes	The primary outcome measure was cognitive (SKT test battery) Tinnitus was a secondary outcome measure, rated on a linear visual analogue scale (0 absent, 10 extremely severe tinnitus)
Notes	This trial was sponsored by Dr. Willmar Schwabe Pharmaceuticals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centre-stratified randomisation in blocks of 4 was performed by the sponsor's biometrics unit using a validated computer program that linked ascending drug numbers to active drug or placebo, respectively. The randomisation list was sealed and stored safely at the sponsor's biometrics unit and block length was not disclosed to investigators.
Allocation concealment (selection bias)	Low risk	See above
Blinding (performance bias and detection bias) All outcomes	Low risk	2 parallel treatment arms and carried out in double-blind manner. Drug and placebo tablets were indistinguishable in appearance, packaging and labelling. Drug and placebo were manufactured and supplied by the same company
Incomplete outcome data (attrition bias) All outcomes	Low risk	214 of 218 patients with Alzheimer's and 181 of 182 patients with vascular dementia with full data for analysis
Selective reporting (reporting bias)	Low risk	Data for all variables reported as being measured
Other bias	Unclear risk	—

Rejali 2004

Methods	Randomised, double-blind, placebo-controlled trial
Participants	66 tinnitus patients aged over 18

Rejali 2004 *(Continued)*

	Mean 4.8 years duration
Interventions	3 months of 120 mg Ginkgo biloba or placebo
Outcomes	Change in Tinnitus Handicap Inventory Change in Glasgow Health Status Inventory
Notes	Poor return rate for post-treatment audiometry but adequate follow-up data for questionnaires

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was carried out by an independent third party using a card from bag system
Allocation concealment (selection bias)	Low risk	See above
Blinding (performance bias and detection bias) All outcomes	Low risk	The study was double-blind. All tablets were provided by the same company
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	31 of 33 in the Gingko group and 29 of 33 in the placebo group completed 7 of 31 in the Gingko group and 17 of 29 in the placebo group did not return for follow-up audiometry: incomplete data for audiometry, so data not included in systematic review
Selective reporting (reporting bias)	Low risk	Data for audiometry not reported All data for principal subjective outcome measures using validated questionnaires are present

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Arrigo 1986	ALLOCATION: Randomised controlled trial PARTICIPANTS: 90 patients, mean age 66 with cognitive insufficiency; no details of subgroup of patients with tinnitus INTERVENTIONS: 120 mg EGb761 versus placebo, 45 days treatment with 15 day washout, cross-over study OUTCOME MEASURES: Unreliable outcome measure. Results for subgroup of patients with tinnitus not separately available.
Bruchert 1991	ALLOCATION: Sequential allocation, no blinding. High attrition rate: 303 patients randomised, 94 patients withdrawn from analysis because of protocol violation.
Eckmann 1982	ALLOCATION:

Study	Reason for exclusion
	No detail of allocation, blinding adequate PARTICIPANTS: 50 patients with cognitive insufficiency; tinnitus only present in 32 INTERVENTIONS: 120 mg Tebonin Forte versus placebo for 30 days OUTCOME MEASURES: Unreliable outcome measure. Tinnitus was only a single symptom of multiple measures. No separate data were available for patients with tinnitus at onset of trial.
Halama 1988	ALLOCATION: Randomised controlled trial. Computer-generated random number. Good blinding technique. PARTICIPANTS: 40 patients > 55 years with cognitive insufficiency. Numbers of patients with tinnitus not specified. INTERVENTIONS: 120 mg Ginkgo biloba extract versus placebo for 12 weeks OUTCOME MEASURES: Tinnitus was only a single symptom of multiple measures. No separate data were available for patients with tinnitus at onset of trial. Published report only stated a positive treatment effect with a P value. No numerical results were given in the text. The pharmaceutical company (Schwabe) declined supply the raw data necessary for full analysis.
Halama 1991	ALLOCATION: Randomised controlled trial. Random number generation. Blinding adequate. PARTICIPANTS: 50 patients, mean age 59 years with ICD-10 diagnosis of dementia. Only 13 patients with tinnitus at onset. INTERVENTIONS: 150 mg Ginkgo biloba extract for 12 weeks versus placebo OUTCOME MEASURES: Unreliable outcome measure. Tinnitus was only a single symptom of multiple measures. No separate data were available for patients with tinnitus at onset of trial.
Holgers 1994	ALLOCATION: Double-blind, placebo-controlled. 20 patients who had already reported benefit in treatment of tinnitus with Ginkgo biloba extract from a larger open study of 80 patients.
Meyer 1986	ALLOCATION: Randomised controlled trial. Allocation concealment unclear. Attrition rate unclear. Adequate blinding. PARTICIPANTS: 103 patients, mean age 50. Tinnitus less than 1 year. Marked inter-group difference in severity of tinnitus at trial onset. No drop-out data given.
Morgenstern 2001	ALLOCATION: Randomised controlled trial. Allocation concealment unclear. Very high attrition. Only 18 of original 52 patients completed study. PARTICIPANTS: All patients treated with 200 mg per day of intravenous EGb761 prior to randomisation into placebo/experimental group

Study	Reason for exclusion
Novotny 1999	ALLOCATION: Allocation concealment unclear (author contacted but did not clarify in response) PARTICIPANTS: 30 tinnitus patients. Half of patients suffering with active Ménière's disease. INTERVENTIONS: 120 mg Ginkgo biloba extract for 12 weeks OUTCOME MEASURES: Inadequate assessment: mild/moderate/severe categorical scale only
Schmidt 1991	ALLOCATION: Randomised controlled trial, double-blind PARTICIPANTS: 99 patients with cognitive insufficiency INTERVENTIONS: 12 weeks of placebo or 150 mg Ginkgo biloba OUTCOME MEASURES: Tinnitus rated as present or absent. Published data only in graphical format report of significance. Raw data could not be obtained from authors.
von Wedel 1995	ALLOCATION: Allocation concealment inadequate - allocated by distribution, not randomisation. Attrition bias. Patients were excluded because their symptoms became worse on treatment.

ICD-10: International Classification of Diseases (10th revision)

APPENDICES

Appendix 1. Search strategies

CENTRAL	PubMed	EMBASE (Ovid)
#1 GINKGO BILOBA single term (MeSH) #2 GINKGO* OR GINGKO* OR GINGKCO* OR GINKO* OR GINGHO OR GINCOSAN OR BILOBALID* OR TEBONIN* OR KAVERI* OR TANAKAN OR TANAKENE OR TEBOKAN OR ROKAN OR SUPERGIN* OR EGB* OR LI NEXT 1370 #3 #1 OR #2 #4 HEARING DISORDERS explode all trees (MeSH) #5 TINNIT* #6 EAR* NEAR BUZZ* OR EAR* NEAR RING* OR EAR* NEAR ROAR* OR EAR* NEAR CLICK* OR EAR* NEAR PULS* #7 #4 OR #5 OR #6 #8 #3 AND #7	#1 "Gingko Biloba" [Mesh] OR GINKGO* [tiab] OR GINGKO* [tiab] OR GINGKCO [tiab] OR GINKO* [tiab] OR GINGHO [tiab] OR GINCOSAN [tiab] OR BILOBALID* [tiab] OR TEBONIN [tiab] OR KAVERI* [tiab] OR TANAKAN [tiab] OR TANAKENE [tiab] OR TEBOKAN [tiab] OR ROKAN [tiab] OR SUPERGIN* [tiab] OR EGB* [tiab] OR "LI 1370" [tiab] #2 "HEARING DISORDERS" [Mesh] OR tinnit* [tiab] OR (EAR* [tiab] AND (BUZZ* [tiab] OR RING* [tiab] OR ROAR* [tiab] OR CLICK* [tiab] OR PULSAT* [tiab] OR PULSE* [tiab])) #3 #1 AND #2	1 ginkgo biloba/ or ginkgo biloba extract/ 2 (GINKGO* or GINGKO* or GINGKCO or GINKO* or GINGHO or GINCOSAN or BILOBALID* or TEBONIN or TEBOKAN or KAVERI* or TANAKAN or TANAKENE or ROKAN or SUPERGIN* or EGB* or (LI adj "1370")).tw. 3 1 or 2 4 tinnitus/ 5 tinnit*.tw. 6 (EAR* and (BUZZ* or RING* or ROAR* or CLICK* or PULSAT* or PULSE*)).tw. 7 6 or 4 or 5 8 3 and 7

(Continued)

CINAHL (EBSCO)	Web of Science/BIOSIS Previews (Web of Knowledge)	CAB Abstracts (Ovid)
S1 (MH "Ginkgo Biloba") S2 TX GINKGO* or GINGKO* or GINGKCO or GINKO* or GINGHO or GINCOSAN or BILOBALID* or TEBONIN or TEBOKAN or KAVERI* or TANAKAN or TANAKENE or ROKAN or SUPERGIN* or EGB* S3 S1 or S2 S4 (MH "Hearing Disorders+") S5 TX tinnit* S6 TX ear* and TX (BUZZ* or RING* or ROAR* or CLICK* or PULSAT* or PULSE*) S7 S4 or S5 or S6 S8 S3 and S7	#1 TS=tinnit* #2 TS=(GINKGO* or GINGKO* or GINGKCO or GINKO* or GINGHO or GINCOSAN or BILOBALID* or TEBONIN or TEBOKAN or KAVERI* or TANAKAN or TANAKENE or ROKAN or SUPERGIN* or EGB*) #3 #2 AND #1	1 (GINKGO* or GINGKO* or GINGKCO or GINKO* or GINGHO or GINCOSAN or BILOBALID* or TEBONIN or TEBOKAN or KAVERI* or TANAKAN or TANAKENE or ROKAN or SUPERGIN* or EGB* or (LI adj "1370")).tw. 2 tinnit*.tw. 3 (EAR* and (BUZZ* or RING* or ROAR* or CLICK* or PULSAT* or PULSE*)).tw. 4 2 OR 3 5 1 AND 4

WHAT'S NEW

Date	Event	Description
8 November 2012	New citation required and conclusions have changed	One new study included (Napryeyenko 2009). Review conclusions updated. Change to the review authors.
12 March 2012	New search has been performed	New searches run.

HISTORY

Protocol first published: Issue 4, 2002
Review first published: Issue 2, 2004

Date	Event	Description
22 September 2009	New search has been performed	New searches run. No new studies to include or exclude.
21 October 2008	Amended	Converted to new review format.
21 February 2007	New search has been performed	New searches run. Updated in Issue 2, 2007.

CONTRIBUTIONS OF AUTHORS

Malcolm P Hilton: planning and writing the protocol.
Emma L Stuart: planning the protocol.

Malcolm Hilton performed the database searching and trial retrieval for the original review. MPH and ELS contributed equally in determining trial eligibility in the original review, data extraction and analysis and review authorship.

Eleanor F Zimmermann: in the 2012 update contributed in determining trial eligibility, data extraction, analysis and updating the contents of the review.

William T Hunt: in the 2012 update contributed in determining trial eligibility, data extraction, analysis and updating the contents of the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- None, Not specified.

External sources

- None, Not specified.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The Background section (Description of the condition) was revised in 2009 to incorporate the standard background section developed by the Cochrane Ear, Nose & Throat Disorders Group.

At the 2012 update of the review we adopted the 'Risk of bias' tool for the assessment of included study quality.

INDEX TERMS

Medical Subject Headings (MeSH)

*Phytotherapy; Dementia [drug therapy]; Ginkgo biloba [*chemistry]; Plant Extracts [*therapeutic use]; Randomized Controlled Trials as Topic; Tinnitus [*drug therapy]

MeSH check words

Adult; Humans