Effectiveness of *Ginkgo biloba* in treating tinnitus: double blind, placebo controlled trial

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Abstract

Objective To determine whether *Ginkgo biloba* is effective in treating tinnitus.
Design Double blind, placebo controlled trial using postal questionnaires.
Participants 1121 healthy people aged between 18 and 70 years with tinnitus that was comparatively stable; 978 participants were matched (489 pairs).
Intervention 12 weeks' treatment with either 50 mg *Ginkgo biloba* extract LI 1370 three times daily or placebo.
Main outcome measures Participants' assessment of tinnitus before, during, and after treatment. Questionnaires included items assessing perception of how loud and how troublesome tinnitus was. Changes in loudness were rated on a six point scale. Changes in how troublesome were rated on a five point scale.
Results There were no significant differences in primary or secondary outcome measures between the groups. 34 of 360 participants receiving active treatment reported that their tinnitus was less troublesome after 12 weeks of treatment compared with 35 of 360 participants who took placebo.
Conclusions 50 mg *Ginkgo biloba* extract LI 1370 given 3 times daily for 12 weeks is no more effective than placebo in treating tinnitus.

Introduction

Tinnitus, or "ringing in the ears," is a common condition recognised as a problem by about 10% of the population and considered a major problem by about 0.5%.[1] There are no effective pharmacological treatments for tinnitus. Because tinnitus is considered to have a number of underlying causes, it is unlikely that a single treatment will be effective for all patients. Therefore, trials of treatments for tinnitus need to be capable of identifying treatments that may help only a subgroup of those with tinnitus. Such trials should be well controlled and include large numbers of patients. Previous trials have failed to meet these criteria and have produced inconsistent and ambiguous results.[2]

Extracts from the *Ginkgo biloba* tree have been used in Chinese medicine for thousands of years. Recently, however, *Ginkgo biloba* extracts have become commonly available in health food stores throughout the United Kingdom; *Ginkgo biloba* is one of the top 10 selling herbs in health food stores in the United States.[3] High quality, standardised extracts from the leaves of the tree have been shown to have significant therapeutic effect on the symptoms of cerebral insufficiency, including memory disturbances and other cognitive deficits such as tinnitus.[4 5]

Prospective studies carried out to determine whether the extract is effective in treating tinnitus without accompanying symptoms of cerebral insufficiency have provided inconsistent results.[2] None the less, *Ginkgo biloba* is frequently suggested as a possible treatment for tinnitus in the press, and many people with tinnitus are using a variety of products on the basis of limited evidence.

In this study a standardised extract of *Ginkgo biloba* (LI 1370, Lichtwer Pharma, Berlin, Germany) was used in a large, controlled trial to determine whether it is effective in treating tinnitus. This is one of the most popular brands sold in the United Kingdom, and the extract conforms to the requirements of the German Commission E monograph.[6]

Participants and methods

Participants

Participants were recruited through advertisements in the national press in the United Kingdom and the British Tinnitus Association's publication, *Quiet*. Altogether, 1121 participants were selected from the original 8667 applicants and matched when possible for sex, age (≤10 years difference), and the duration of tinnitus (≤5 years). (Details of the exclusion criteria can be found on the *BMJ*'s website.)

Methods

This double blind, placebo controlled trial was carried out entirely by mail and telephone. All procedures were approved by the local ethics committee (South Birmingham Health Authority). Assuming that there would be a significant improvement in tinnitus in 30% of participants taking placebo, the calculations predicted that it would be necessary to have 496 patients in each group to show a 10% improvement over placebo among those taking active treatment with a power of 90% at the 0.05 significance level.[7] The sample size was set to account for withdrawals.

Participants were paired and then allocated two numbers from a randomly arranged code. One number corresponded to placebo treatment and one to active treatment.

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Tinnitus was assessed subjectively using questionnaires, and no audiological measurements were taken. The first questionnaire was completed before treatment began, the second after 4 weeks of treatment, the third after the end of 12 weeks of treatment, and the fourth 2 weeks after treatment ended.

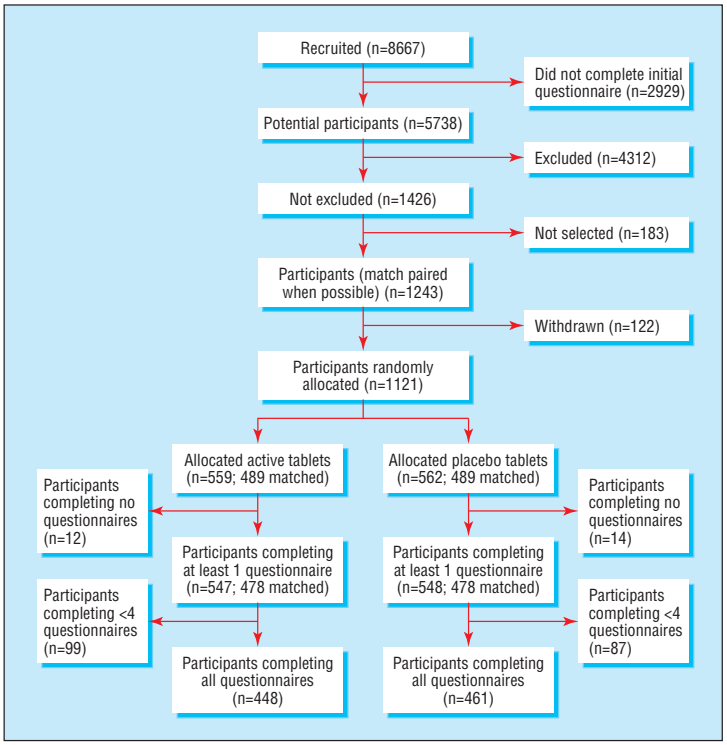
Intervention

The treatment was provided as 252 tablets containing 50 mg of either *Ginkgo biloba* standardised extract LI 1370 (containing 25% flavonoids, 3% ginkgolides, and 5% bilobalides) or placebo (both provided by Lichtwer Pharma). Participants were instructed to take three tablets daily for 12 weeks.

Outcome measures

The scales used in the questionnaires were devised for this study and based on previously validated self assessment scales.[8] The questionnaires contained 21 questions about the severity of tinnitus. These were divided into three groups and summary scores were produced for each group. These scores ranged from 0 to 12 for measures of loudness, from 0 to 22 for measures of awareness and ability to ignore, and from 0 to 39 for impact. The sum of the scores in these three groups was the total summary score. A summary score of 0 indicates that a participant has no tinnitus. The maximum summary score of 73 indicates that a participant has tinnitus that is severely troublesome—for example, it is always very loud, the participant can never ignore it, and it has a large impact on the participant's life.

In the second, third, and fourth questionnaires there were three additional questions about changes in tinnitus. Participants were asked to score changes in the loudness of their tinnitus on a six point scale ranging from −4 (treatment has made tinnitus much louder) to 6 (treatment has made it disappear).



Progress of participants through the trial

Table 1 Characteristics of participants

	Treatment group	
	Active (n=489)	Placebo (n=489)
Mean (SD) age (years)	52.9 (9.3)	53.0 (9.3)
Mean (SD) duration of tinnitus (years)	10.0 (8.3)	10.1 (8.3)
No (%) men	338 (69)	338 (69)
No (%) women	151 (31)	151 (31)
Mean (SD) summary score for compliance*	7.2 (1.5)	7.3 (1.4)

*Scores for compliance ranged from 0 (instructions not followed well) to 8 (instructions followed well).

Changes in the amount of trouble caused were scored on a five point scale ranging from −4 (treatment has made tinnitus much more troublesome) to 4 (treatment has made it much less troublesome). The score for "no change" was in the middle or near the middle of the scale.

The questions on change in tinnitus were the primary outcome measures for the trial, and the scores of tinnitus severity were used as secondary outcome measures.

Additional questions about the variability of tinnitus, symptoms of cerebral insufficiency other than tinnitus, compliance with the treatment regimen, and side effects were also included. Scores for compliance with treatment ranged from 0 (instructions not followed well) to 8 (instructions followed well).

Data analysis

Data were analysed on an intention to treat basis wherever possible. Data entry and initial analyses were carried out by a researcher blinded to the participant's allocation. Statistical analysis was carried out using SPSS version 9.0 for Windows except for the calculation of confidence intervals for proportions.[9] All reported P values are two tailed. Paired data were compared between treatment groups using McNemar's test and paired sample *t* tests. Unmatched analyses did not provide any additional information and have therefore been excluded from this paper.

Results

Altogether 1121 participants were allocated to treatment (559 to active treatment and 562 to placebo) (figure); of these, 956 participants were paired. Characteristics of the paired participants are shown in table 1. Analysis of the side effects of treatment was carried out using data from all 489 matched pairs. However, 26 participants completed no questionnaires so all other analyses were carried out on the remaining 478 pairs in which both members completed at least one questionnaire.

Outcome measures

There were no significant differences between the treatment groups at weeks 4, 12, and 14 with respect to primary outcome measures (table 2), secondary outcome measures, compliance, or cerebral insufficiency. Additional details are available on the *BMJ*'s website.

The incidence of adverse events, such as gastrointestinal upset (about 3%), dizziness (about 1%), mouth dryness (about 1%), and other events (each $<1\%$), was similar between the treatment groups, but

Table 2 Paired comparison of the No and proportion of pairs in each group (active treatment or placebo) reporting an improvement in tinnitus. Treatment was considered to have been successful if participants reported an improvement at 4 or 12 weeks or a worsening at 14 weeks (2 weeks after stopping treatment)

Time (No of pairs)	Neither treatment successful	Active treatment unsuccessful/ placebo successful	Active treatment successful/ placebo unsuccessful	Both active and placebo successful	Proportion of treatment successful (%)		95% CI*	McNemar's test
					Placebo	Active		
4 weeks (414)	367	27	18	2	7.0	4.8	–5.3 to 1.0	0.2
12 weeks (360)	292	34	33	1	9.7	9.4	–4.7 to 4.2	1.0
14 weeks (354)	275	32	40	7	11.0	13.3	–2.4 to 7.0	0.4

*Comparison between results of active treatment and placebo treatment.

the incidence of beneficial effects was not. One or more beneficial effects, such as improvements in general wellbeing, circulation, and hearing, were reported by 24/489 (4.9%) participants in the active treatment group and 11/489 (2.2%) in the placebo group. This difference was statistically significant (95% confidence interval 0.4% to 4.9%). Subgroup analyses failed to find any significant differences between groups with respect to different types of beneficial effects.

Discussion

Ginkgo biloba extract LI 1370 had no greater therapeutic effect than placebo in treating tinnitus. In addition, other symptoms of cerebral insufficiency were not significantly affected by the treatment. The results from this trial are similar to some reports and contrast with others.[2] The main strength of this study was its large size and controlled design. Previous trials involved fewer than 300 subjects and often lacked adequate controls.[2] This study achieved its large sample size using a simple approach to data collection (postal questionnaires).

Methods of assessing tinnitus have differed between trials, although most have used a simple, subjective measurement of change in tinnitus, similar to the primary outcome measure used in this study. Our method of assessing tinnitus was thorough, enabled small changes to be identified, and concentrated on the most clinically relevant measurement for this condition (that is, perceived changes in tinnitus). Another strength of this study was that this treatment regimen has been shown to be effective in cerebral insufficiency. Additionally, a measure of the symptoms of cerebral insufficiency was included in the design to determine whether any improvements in tinnitus were associated with improvements in symptoms of cerebral insufficiency.

Most previous trials have used similar treatment doses and been of similar duration, but the methods of administration and the composition of the extract have varied.[5] Therefore, it is possible that at least some of the inconsistencies identified by previous studies may be related to the different types of *Ginkgo biloba* extract that were used. Measurements of other symptoms of cerebral insufficiency have not been made in previous trials. Since neither tinnitus nor other symptoms of cerebral insufficiency were significantly improved in this study, it would be interesting to learn whether trials in which *Ginkgo biloba* was found to be effective in tinnitus showed that participants had any improvements in other symptoms of cerebral insufficiency. It is tempting to speculate that positive trials have involved a greater number of patients who have cerebral insufficiency and thus improvements in tinnitus were related to an improvement in cerebral insufficiency rather than being a direct effect of treatment.

What is already known on this topic

Ginkgo biloba extract has been shown to have therapeutic effects on symptoms of cerebral insufficiency including memory disturbances and other cognitive deficits, such as tinnitus

Whether it is effective in treating tinnitus alone (without other accompanying symptoms of cerebral insufficiency) is not clear

Previous studies were small, often poorly controlled, and have had inconsistent results

What this study adds

This large, double blind, placebo controlled trial found that *Ginkgo biloba* extract was no more effective than placebo in treating tinnitus alone

The extract used in this study (LI 1370 150 mg/day for 12 weeks) seems to be ineffective in treating tinnitus alone, but it may be effective in treating tinnitus in patients who also have other symptoms of cerebral insufficiency. The composition of other extracts or the use of other treatment regimens, or both, might be effective in treating tinnitus alone but there is little evidence of this.

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