National Institute for Health and Care Excellence

Final

Tinnitus: assessment and management

[N] Evidence review for betahistine

NICE guideline NG155

Intervention evidence review

March 2020

Final

This evidence review was developed by the National Guideline Centre

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1 Betahistine

1.1 Review question: What is the clinical and cost effectiveness of betahistine for people with tinnitus?

1.2 Introduction

There is currently no drug licensed in the UK for the treatment of tinnitus. Betahistine, a drug used to treat the balance symptoms associated with Meniere's disease, contains betahistine dihydrochloride or betahistine dimesylate, a strong H3 antagonist and a weak H1 agonist. It is suggested to increase the circulation of the inner ear. It is not licensed for such use.

The aim of this review question is to determine whether betahistine is clinically and cost-effective for the management of tinnitus.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	Children, young people and adults with tinnitus. Strata: • Those taking betahistine for tinnitus • Those taking betahistine for the tinnitus-aspect of Meniere's disease [It should be noted that betahistine tablets are not recommended for use in children and adolescents below age 18 years due to lack of data on safety and efficacy]
Intervention(s)	• Betahistine (any dose regimes or formulations for any duration of treatment)
Comparison(s)	• Control group (no treatment/waiting list) • Placebo
Outcomes	• Tinnitus severity (critical) Impact of tinnitus (critical): • Tinnitus distress • Tinnitus annoyance Health related QoL(critical): • QoL (tinnitus) • QoL Tinnitus percept (important): • Tinnitus loudness Other co-occurring complaints (important): • Depression • Anxiety

	• Anxiety and depression • Sleep Adverse events (important): • Safety • Tolerability • Side effects
Study design	• RCT • Systematic review of RCTs • If there is an inadequate amount of RCT data, non-randomised comparative studies will be considered.

1.4 Clinical evidence

1.4.1 Included studies

A Cochrane review of betahistine for tinnitus with 5 studies[23] was included in its entirety as it matched our protocol for the strata of people with tinnitus without Meniere's Disease strata. The methods of data analysis and quality assessment for this part of the review are therefore in accordance with the methods described in the Cochrane review.

NICE methods include the avoidance of an overall risk of bias assessment of "unclear", whilst Cochrane methods allow the use of "unclear". For the included Cochrane review, the Cochrane 'risk of bias' tool in Review Manager 5.3 was used for risk of bias assessments, whereas NICE methods include the use of Cochrane 'risk of bias' 2.0 tool. For data analysis, NICE methods consist of the use of Peto odds ratio analyses where there are zero events in either arm or a less than 1% event rate. Cochrane reviews however include the use of risk ratio analyses where there are zero events in both arms of included studies. Additionally, Cochrane selected different populations for potential subgroup analyses to investigate heterogeneity (see Appendix A: for our selected subgroup populations). The subgroups selected by Cochrane authors were: age (children < 16 or 18 years and adults ≥ 16 or 18 years); duration of tinnitus (acute ≤ 3 months and chronic > 3 months); dose of betahistine administered (minimum daily dose of 8 mg to a maximum of 148 mg); additional interventions (betahistine with and without an additional intervention).

One further randomised controlled trial that was outside the scope of the Cochrane review was also included in our review.[1] This study investigated betahistine in people with Meniere's disease and reported data on tinnitus quality of life.

The included studies are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summaries below (Table 3 and Table 4).

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix F.

1.4.2 Excluded studies

One Cochrane review was excluded[5] as it was investigating betahistine for Meniere's disease or syndrome and some of the included studies did not report on tinnitus-related outcomes. The studies included in this review were checked for inclusion in our review, but all were excluded.

See the excluded studies list in appendix H.

1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Wegner 2018[23] (Çekkayan 1996[3], Kay 1981[7], Ma 2006[9], Mashali 2016[12], Maqbool 2010[11])	Systematic review comparing betahistine with placebo, no intervention or education and information. Five studies were included: Four compared betahistine with placebo, without concurrent medication in either arm. One compared betahistine with placebo, with concurrent medication (flunarizine hydrochloride) in both arms.	Total n=303 or 305 (unclear) The review included studies of patients of any age with acute or chronic subjective idiopathic tinnitus. Studies of people with Meniere's Disease were excluded. Age (range of means): 40 to 50 years Gender: Not reported overall Duration of tinnitus (range): Not reported overall. Various countries (Turkey, England, China, Pakistan, Iran).	<u>Betahistine versus placebo without concurrent medication (four studies):</u> Tinnitus loudness (follow up: 1 month): measured using VAS, scale range unclear Tinnitus loudness (follow up: 2 months): measured using VAS, scale range 0-10 Change in tinnitus loudness (follow up: 28 days): measured using VAS, scale unclear Change in tinnitus severity (follow up: 12 weeks): measured by Tinnitus Severity Index, scale range 0-56 Tinnitus severity (follow up: 3 months): measured by Tinnitus Severity Score/Scale, scale range 0 to 4 Significant adverse events (follow up: 28 days) Significant adverse events (follow up: 3 months) Other adverse events (follow up: 28 days)	

Study	Intervention and comparison	Population	Outcomes	Comments
			Other adverse events (follow up: 3 months) <u>Betahistine versus placebo with concurrent medication (one study):</u> Change in tinnitus match (follow up: 1 week): measured using bespoke scale, scale range 0 to 5 Significant adverse events (follow up: 1 week) Other adverse events (follow up: 1 week)	
BEMED trial: Adrion 2016[1]	Intervention (n=73) Betahistine, 24mg twice per day. Comparison (n=74) Placebo.	n=147 People with a diagnosis of definite unilateral or bilateral Meniere's disease, fulfilling the criteria of the 1995 American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) guideline. People must have been in an active stage of the disease. Age (mean (SD)): Placebo - 54.5 (12.8), Betahistine - 56.1 (11.1)	Change in quality of life (follow up: 9 months): measured by Mini-Tinnitus Questionnaire (mini-TQ), scale range unclear	This study had two betahistine arms. Only the "low dose" arm has been extracted for this review as the "high dose" arm uses doses that are above the maximum licensed dose in the UK.

Study	Intervention and comparison	Population	Outcomes	Comments
		Gender (male to female ratio): 74:73 Duration of tinnitus: not reported Germany		

See appendix D for full evidence tables.

1.4.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: Betahistine (without concurrent medication) versus placebo in people with tinnitus (without Meniere's disease)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Betahistine (without concurrent medication) (95% CI)
Tinnitus loudness visual analogue scale. Scale from: 0 to 10.	81 (2 studies) 1 months	⨁⊖⊖⊖ VERY LOW[1] due to risk of bias, inconsistency, indirectness, imprecision		The mean tinnitus loudness ranged across control groups from 4.8 to 8.5	The mean tinnitus loudness in the intervention groups was 0.16 lower (1.01 lower to 0.7 higher)
Tinnitus loudness visual analogue scale. Scale from: 0 to 10.	70 (1 study) 2 months	⨁⊖⊖⊖ VERY LOW[2] due to risk of bias, indirectness, imprecision		The mean change in tinnitus loudness in the control groups was 4.46	The mean change in tinnitus loudness in the intervention groups was 0.39 lower (1.37 lower to 0.6 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Betahistine (without concurrent medication) (95% CI)
Change in tinnitus loudness visual analogue scale. Scale from: 0 to 10.	11 (1 study) 28 days	⨁⊖⊖⊖ VERY LOW[3] due to risk of bias, indirectness, imprecision		The mean tinnitus loudness in the control groups was 0.83	The mean tinnitus loudness in the intervention groups was 0.43 lower (1.2 lower to 0.34 higher)
Change in tinnitus severity Tinnitus Severity Index. Scale from: 0 to 56.	50 (1 study) 12 weeks	⨁⨁⨁⊖ MODERATE[4] due to risk of bias		The mean change in tinnitus severity in the control groups was 1.68	The mean change in tinnitus severity in the intervention groups was 0.02 higher (1.05 lower to 1.09 higher)
Tinnitus severity tinnitus severity score/scale. Scale from: 0 to 4.	36 (1 study) 3 months	⨁⨁⊖⊖ LOW[5] due to risk of bias, imprecision		The mean tinnitus severity in the control groups was 3.13	The mean tinnitus severity in the intervention groups was 0.52 lower (1.34 lower to 0.3 higher)
Significant adverse effects	11 (1 study) 28 days	⨁⊖⊖⊖ VERY LOW[3] due to risk of bias, indirectness, imprecision	Not estimable	See comment[6]	-
Significant adverse effects	41 (1 study) 3 months	⨁⨁⨁⊖ MODERATE[4] due to risk of bias	Not estimable	See comment[6]	-
Other adverse effects	11 (1 study) 28 days	⨁⊖⊖⊖ VERY LOW[3] due to risk of bias,	RR 3.5 (0.17 to 70.94)		-[7]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Betahistine (without concurrent medication) (95% CI)
		indirectness, imprecision			
Other adverse effects	41 (1 study) 3 months	⨁⨁⨁⨀ MODERATE[4] due to risk of bias	Not estimable	See comment[6]	-

[1] Downgraded one level due to an unclear overall risk of bias in both studies; downgraded one level due to inconsistency (one study has a slight preference for betahistine and the other for placebo); downgraded one level due to indirectness (in one study a patient with Meniere's disease was included and in the other studies only male participants/military personnel with noise-induced hearing loss were included); downgraded one level due to imprecision.
[2] Downgraded one level due to an unclear overall risk of bias, downgraded one level due to indirectness (only male participants/ military personnel with noise-induced hearing loss were included); downgraded one level due to imprecision.
[3] Downgraded one level due to an unclear overall risk of bias, downgraded one level due to indirectness (a patient with Meniere's disease was included); downgraded one level due to imprecision.
[4] Downgraded one level due to an unclear overall risk of bias.
[5] Downgraded one level due to an unclear overall risk of bias; downgraded one level due to imprecision.
[6] Zero events in both arms.
[7] Due to zero events in the control arm, absolute effect could not be calculated.

Table 4: Clinical evidence summary: Betahistine (with concurrent medication) versus placebo in people with tinnitus (without Meniere 's disease)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Betahistine (with concurrent medication) (95% CI)
Change in tinnitus loudness match Scale from: 0 to 5.	60 (1 study) 1 weeks	⨁⨁⨁⨀ MODERATE[1] due to risk of bias		The mean change in tinnitus loudness match in the control groups was 2.5	The mean change in tinnitus loudness match in the intervention groups was 0.10 lower (0.5 lower to 0.3 higher)
Significant adverse effects	59 (1 study) 1 weeks	⨁⨁⨀⨀ LOW[3]	RR 3.10 (0.13 to 73.14)		-[2]-

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Betahistine (with concurrent medication) (95% CI)
		due to risk of bias, imprecision			
Other adverse effects	59 (1 study) 1 weeks	⨁⨁⨁⊖ MODERATE[1] due to risk of bias	RR 0.44 (0.13 to 1.55)	333 per 1000	187 fewer per 1000 (from 290 fewer to 183 more)

[1] Downgraded one level due to an unclear overall risk of bias.
[2] Due to zero events in the control arm, absolute effect could not be calculated.
[3] Downgraded one level due to an unclear overall risk of bias; downgraded one level due to imprecision.

Table 5: Clinical evidence summary: Betahistine versus placebo in people with Meniere 's disease

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Betahistine (95% CI)
Quality of life Mini Tinnitus Questionnaire	142 (1 study) 9 months	⨁⨁⨁⨁ HIGH		The mean quality of life in the control groups was 0.121	The mean quality of life in the intervention groups was 0.01 higher (0.13 lower to 0.15 higher)

See appendix F for full GRADE tables.

1.5 Economic evidence

1.5.1 Included studies

No relevant health economic studies were identified.

1.5.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in appendix G.

1.5.3 Unit costs

Table 6: UK costs of betahistine

Drug	Daily dose (*units*)	Cost – per 28 days	Cost – annual
Betahistine (16mg), Initial dose	3	£1.64	£21.39
Betahistine (8mg), Maintenance dose	3	£1.16	£15.13

Source[s]: NHS Drug Tariff [14], BNF [6]

(a) Drug costs for betahistine were sourced from NHS drug tariff [14]. The cost for 84 16mg tablets was £1.64 and £1.16 for 84 8mg tablets. The cost per pill was calculated and the 28 days and annual cost calculated thereafter according to the recommended dose in the BNF[6].

1.6 Evidence statements

1.6.1 Clinical evidence statements

- **Betahistine (without concurrent medication) versus placebo in people with tinnitus (without Meniere's disease)**

All evidence for this comparison came from the Wegner 2018 Cochrane review, with four studies (n=243 to 245) comparing betahistine against placebo without concurrent medication in either arm. For the outcomes of tinnitus severity (critical) and tinnitus loudness (important) there was no clinically important difference between betahistine and placebo. A difference was seen only for the dichotomous outcome 'other adverse effects' at 28 days after treatment, which favoured the placebo, indicating more adverse effects in the betahistine group. However this evidence was taken from the smallest of the four populations analysed (11 participants) and was of Very Low quality due to risk of bias, indirectness and imprecision. Other dichotomous outcomes (significant adverse effects at 28 days and 3 months, and other adverse effects at 3 months) showed no difference.

- **Betahistine (with concurrent medication) versus placebo in people with tinnitus (without Meniere's disease)**

One study (n=60) from the Wegner 2018 Cochrane review compared betahistine against placebo with concurrent medication (flunarizine hydrochloride) in both arms. In this comparison there was no clinically important difference in tinnitus loudness between the two arms (moderate quality evidence). In the only other two outcomes in this comparison there were contrasting results, with Low quality evidence showing that the control was favoured for significant adverse events (i.e. less adverse events in control arm) but Moderate quality evidence showing that betahistine was favoured when considering other adverse events. All three outcomes here were taken at a time point of one week after treatment.

- **Betahistine versus placebo in people with Meniere's Disease**

Evidence for this comparison came from a single study (n=142) with a single outcome of quality of life according to the Mini Tinnitus Questionnaire. This evidence was of a High quality and showed no clinically important difference between betahistine and placebo.

1.6.2 Health economic evidence statements

- No relevant economic evaluations were identified.

1.7 The committee's discussion of the evidence

1.7.1 Interpreting the evidence

1.7.1.1 The outcomes that matter most

Tinnitus distress, annoyance and tinnitus severity were critical outcomes as they were thought to be common factors for people with tinnitus and impact their quality of life. Quality of life (tinnitus-related) and general quality of life were also critical outcomes due to their impact on the person with tinnitus.

Tinnitus loudness, anxiety, depression, sleep, safety, tolerability and side effects were thought to be important outcomes.

1.7.1.2 The quality of the evidence

For people with tinnitus without Meniere's disease (evidence summarised in the Cochrane Review), there were two comparisons; with and without the use of concurrent medication.

Betahistine versus placebo (without concurrent medication)

Outcome data was not reported for the critical outcomes: tinnitus distress, quality of life, tinnitus-related quality of life and tinnitus annoyance. Outcome data was reported for tinnitus loudness, significant adverse effects, other adverse effects and tinnitus severity, across four studies. The overall quality of the evidence ranged from very low to moderate due to risk of bias and imprecision.

Betahistine versus placebo (with concurrent medication)

Outcome data was not reported for any of the critical outcomes. Outcome data was reported for tinnitus loudness and adverse effects within one study. The overall quality of the evidence ranged from low to moderate due to risk of bias and imprecision.

Betahistine versus placebo in people with Meniere's disease

In addition to the Cochrane Review which included five randomised trials, one additional study was included. This study was outside the scope of the Cochrane review which excluded people with Meniere's disease. For the comparison of betahistine versus placebo in people with Meniere's disease, the outcome of quality of life was reported; this evidence was graded high quality.

1.7.1.3 Benefits and harms

There was limited evidence for the two population groups: tinnitus with Meniere's disease and tinnitus without Meniere's disease. The committee noted that some people are occasionally prescribed betahistine to treat tinnitus, but it is not licensed for this. There is currently no clinically proven drug treatment for tinnitus.

The evidence identified in this review showed that there is no clinical difference between betahistine and placebo with some possible harm shown in the group of people with tinnitus and without Meniere's disease. The committee noted that any potential harms in clinical practice are mainly limited to gastrointestinal upset. There was also evidence that there is no clinical difference between betahistine and placebo in people with tinnitus as a symptom of their Meniere's disease for the outcome tinnitus-related quality of life.

The committee agreed that betahistine should not be offered as treatment for tinnitus.

1.7.2 Cost effectiveness and resource use

There were no economic evaluations for this review question. The clinical review concluded that there was no benefit associated with using betahistine as well evidence of adverse effects. Therefore, the committee decided that clinicians should advise people with tinnitus about the limited evidence around betahistine. The committee were of the view that this process would reduce the number of betahistine prescriptions because through joint decision making, the clinician and the person with tinnitus would conclude that the drug may not be an effective treatment option. Betahistine cost between £15 and £21 a year. This drug would not be considered cost-effective on the basis of the existing clinical evidence because it does not show improved health outcomes. As the recommendation could reduce the number of prescriptions of betahistine, the implementation of the recommendation could result in modest cost savings.

1.7.3 Other factors the committee took into account

Betahistine is licenced for use for people with tinnitus associated with Meniere's disease but not for those with just tinnitus. However, betahistine is sometimes used to treat tinnitus in current practice. Consequently, implementation of this recommendation will lead to a change in practice. The committee agreed that implementation will not be challenging and should lead to a modest cost saving. As part of the shared decision making process individuals should also be offered the other management options outlined in the recommendations in this guideline.

Lay members on the committee felt that whilst some people with tinnitus may consult their GP looking for a simple drug regime to reduce their tinnitus, many others, especially those with a number of conditions requiring drug therapy, would be pleased not to be offered further medication.

The committee noted that if a person is already taking betahistine to treat tinnitus, before stopping the medication the prescriber could explain to them that the evidence shows it does not help with symptoms of tinnitus. Any concerns about discontinuing the medication can be discussed.

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Appendices

Appendix A: Review protocols

Table 7: Review protocol: What is the clinical and cost effectiveness of betahistine for the management of tinnitus?

ID	Field	Content
0.	PROSPERO registration number	Not registered
1.	Review title	The clinical and cost effectiveness of betahistine for the management of tinnitus
2.	Review question	What is the clinical and cost effectiveness of betahistine for the management of tinnitus?
3.	Objective	Betahistine is primarily used and licensed for treatment of Meniere's disease but is often taken to relieve tinnitus. It is not licensed for tinnitus in people who do not have Meniere's disease and its use in this way is off-label. The review aims to evaluate betahistine in comparison with control or placebo on clinical and cost-effective outcomes. Recommendations might cover the inclusion of betahistine as part of a package of care for management of tinnitus.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR)

		• Embase • MEDLINE • CINAHL, Current Nursing and Allied Health Literature Searches will be restricted by: • English language • Human studies • Letters and comments are excluded. Other searches: • Inclusion lists of relevant systematic reviews will be checked by the reviewer. The searches may be re-run 6 weeks before final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review
5.	Condition or domain being studied	Tinnitus
6.	Population	Inclusion: Children, young people and adults with tinnitus Strata:

		• Those taking betahistine for tinnitus • Those taking betahistine for the tinnitus-aspect of Meniere's disease [It should be noted that betahistine tablets are not recommended for use in children and adolescents below age 18 years due to lack of data on safety and efficacy] Exclusion: None
7.	Intervention/Exposure/Test	• Betahistine (any dose regimes or formulations for any duration of treatment)
8.	Comparator/Reference standard/Confounding factors	• Control group (no treatment/waiting list) • Placebo
9.	Types of study to be included	• Systematic reviews • RCTs • If there is an inadequate amount of RCT data, non-randomised comparative studies will be considered
10.	Other exclusion criteria	• Non-English language studies • Studies will only be included if they report one or more of the outcomes listed above. • Descriptive (non-comparative) studies will be excluded
11.	Context	N/A
12.	Primary outcomes (critical outcomes)	• Tinnitus severity Impact of tinnitus: • Tinnitus distress

		• Tinnitus annoyance Health related QoL: • QoL (tinnitus) • QoL
13.	Secondary outcomes (important outcomes)	Tinnitus percept: • Tinnitus loudness Other co-occurring complaints: • Depression • Anxiety • Anxiety and depression • Sleep Adverse events: • Safety • Tolerability • Side effects
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened for inclusion. The full text of potentially eligible studies will be retrieved and will be assessed for eligibility in line with the criteria outlined above. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. An in-house developed database; EviBase, will be used for data extraction. A standardised form is followed to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and for undertaking assessment of study quality. Summary evidence tables will be produced including information on: study setting; study population and participant demographics and

		baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings. A second reviewer will quality assure the extracted data. Discrepancies will be identified and resolved through discussion (with a third reviewer where necessary).
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews the following checklist will be used according to study design being assessed: • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and 95% confidence intervals will be calculated for each outcome. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the

		heterogeneity, the results will be presented using random-effects. GRADE pro will be used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. Other bias will only be taken into consideration in the quality assessment if it is apparent. Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. If sufficient data is available to make a network of treatments, WinBUGS will be used for network meta-analysis.
17.	Analysis of sub-groups	• People with profound deafness • People with learning disability or cognitive impairment
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)

19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	29/05/18		
22.	Anticipated completion date	11/03/20		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☐	☑
		Piloting of the study selection process	☐	☑
		Formal screening of search results against eligibility criteria	☐	☑
		Data extraction	☐	☑
		Risk of bias (quality) assessment	☐	☑
		Data analysis	☐	☑

24.	Named contact	**5a. Named contact** National Guideline Centre **5b Named contact e-mail** Tinnitus@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and the National Guideline Centre
25.	Review team members	From the National Guideline Centre: • Dr Jennifer Hill [Guideline lead] • Ms Sedina Lewis/Ms Julie Neilson [Senior systematic reviewers] • Dr Richard Clubbe [Systematic reviewer] • Mr David Wonderling [Health economist lead] • Mr Emtiyaz Chowdhury [Health economist] • Ms Jill Cobb [Information specialist] • Dr Giulia Zuodar [Project manager]
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered

		by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].
29.	Other registration details	N/A
30.	Reference/URL for published protocol	N/A
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Tinnitus, betahistine
33.	Details of existing review of same topic by same authors	N/A
34.	Current review status	☐ Ongoing ☒ Completed but not published

		☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	N/A
36.	Details of final publication	www.nice.org.uk

Table 8: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2003, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[13] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline

committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:

- The more recent the study, the more applicable it will be.
- Studies published in 2003 or later but that depend on unit costs and resource data entirely or predominantly from before 2003 will be rated as ‘Not applicable’.
- Studies published before 2003 will be excluded before being assessed for applicability and methodological limitations.

Quality and relevance of effectiveness data used in the health economic analysis:

- The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[13]

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 4: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 02 April 2019	Exclusions
Embase (OVID)	1974 – 02 April 2019	Exclusions
The Cochrane Library (Wiley)	Cochrane Reviews to 2019 Issue 4 of 12 CENTRAL to 2019 Issue 4 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 4 of 4	None
CINAHL, Current Nursing and Allied Health Literature (EBSCO)	Inception – 02 April 2019	Exclusions

Medline (Ovid) search terms

1.	Tinnitus/
2.	tinnit*.ti,ab.
3.	1 or 2
4.	letter/
5.	editorial/
6.	news/
7.	exp historical article/
8.	Anecdotes as Topic/
9.	comment/
10.	case report/
11.	(letter or comment*).ti.
12.	or/4-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animals/ not humans/
16.	exp Animals, Laboratory/
17.	exp Animal Experimentation/
18.	exp Models, Animal/

19.	exp Rodentia/
20.	(rat or rats or mouse or mice).ti.
21.	or/14-20
22.	3 not 21
23.	limit 22 to English language

Embase (Ovid) search terms

1.	tinnitus/
2.	tinnit*.ti,ab.
3.	1 or 2
4.	letter.pt. or letter/
5.	note.pt.
6.	editorial.pt.
7.	Case report/ or Case study/
8.	(letter or comment*).ti.
9.	or/4-8
10.	randomized controlled trial/ or random*.ti,ab.
11.	9 not 10
12.	animal/ not human/
13.	Nonhuman/
14.	exp Animal Experiment/
15.	exp Experimental animal/
16.	Animal model/
17.	exp Rodent/
18.	(rat or rats or mouse or mice).ti.
19.	or/11-18
20.	3 not 19
21.	limit 20 to English language

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Tinnitus] explode all trees
#2.	tinnit*:ti,ab
#3.	#1 or #2

CINAHL (EBSCO) search terms

S1.	(MH "Tinnitus")
S2.	(MH "Tinnitus Retraining Therapy")
S3.	tinnit*
S4.	S1 OR S2 OR S3
S5.	PT anecdote or PT audiovisual or PT bibliography or PT biography or PT book or PT book review or PT brief item or PT cartoon or PT commentary or PT computer program or PT editorial or PT games or PT glossary or PT historical material or PT interview or PT letter or PT listservs or PT masters thesis or PT obituary or PT pamphlet or PT pamphlet chapter or PT pictorial or PT poetry or PT proceedings or PT “questions and answers” or PT response or PT software or PT teaching materials or PT website
S6.	S4 NOT S5

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to the tinnitus population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics and quality of life studies.

Table 5: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2002 – 02 March 2019	Exclusions Health economics studies Quality of life studies
Embase	2002 – 02 March 2019	Exclusions Health economics studies Quality of life studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 31 Mar 2018 NHSEED - Inception to March 2015	None

Medline (Ovid) search terms

1.	Tinnitus/
2.	tinnit*.ti,ab.
3.	1 or 2
4.	letter/
5.	editorial/
6.	news/
7.	exp historical article/
8.	Anecdotes as Topic/
9.	comment/
10.	case report/
11.	(letter or comment*).ti.
12.	or/4-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animals/ not humans/
16.	exp Animals, Laboratory/
17.	exp Animal Experimentation/
18.	exp Models, Animal/
19.	exp Rodentia/
20.	(rat or rats or mouse or mice).ti.
21.	or/14-20
22.	3 not 21
23.	limit 22 to English language
24.	Economics/
25.	Value of life/

26.	exp "Costs and Cost Analysis"/
27.	exp Economics, Hospital/
28.	exp Economics, Medical/
29.	Economics, Nursing/
30.	Economics, Pharmaceutical/
31.	exp "Fees and Charges"/
32.	exp Budgets/
33.	budget*.ti,ab.
34.	cost*.ti.
35.	(economic* or pharmaco?economic*).ti.
36.	(price* or pricing*).ti,ab.
37.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
38.	(financ* or fee or fees).ti,ab.
39.	(value adj2 (money or monetary)).ti,ab.
40.	or/24-39
41.	quality-adjusted life years/
42.	sickness impact profile/
43.	(quality adj2 (wellbeing or well being)).ti,ab.
44.	sickness impact profile.ti,ab.
45.	disability adjusted life.ti,ab.
46.	(qal* or qtime* or qwb* or daly*).ti,ab.
47.	(euroqol* or eq5d* or eq 5*).ti,ab.
48.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
49.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
50.	(hui or hui1 or hui2 or hui3).ti,ab.
51.	(health* year* equivalent* or hye or hyes).ti,ab.
52.	discrete choice*.ti,ab.
53.	rosser.ti,ab.
54.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
55.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
56.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
57.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
58.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
59.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
60.	or/41-59
61.	23 and (40 or 60)

Embase (Ovid) search terms

1.	tinnitus/
2.	tinnit*.ti,ab.
3.	1 or 2
4.	letter.pt. or letter/
5.	note.pt.
6.	editorial.pt.

7.	Case report/ or Case study/
8.	(letter or comment*).ti.
9.	or/4-8
10.	randomized controlled trial/ or random*.ti,ab.
11.	9 not 10
12.	animal/ not human/
13.	Nonhuman/
14.	exp Animal Experiment/
15.	exp Experimental animal/
16.	Animal model/
17.	exp Rodent/
18.	(rat or rats or mouse or mice).ti.
19.	or/11-18
20.	3 not 19
21.	health economics/
22.	exp economic evaluation/
23.	exp health care cost/
24.	exp fee/
25.	budget/
26.	funding/
27.	budget*.ti,ab.
28.	cost*.ti.
29.	(economic* or pharmaco?economic*).ti.
30.	(price* or pricing*).ti,ab.
31.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
32.	(financ* or fee or fees).ti,ab.
33.	(value adj2 (money or monetary)).ti,ab.
34.	or/21-33
35.	quality adjusted life year/
36.	"quality of life index"/
37.	short form 12/ or short form 20/ or short form 36/ or short form 8/
38.	sickness impact profile/
39.	(quality adj2 (wellbeing or well being)).ti,ab.
40.	sickness impact profile.ti,ab.
41.	disability adjusted life.ti,ab.
42.	(qal* or qtime* or qwb* or daly*).ti,ab.
43.	(euroqol* or eq5d* or eq 5*).ti,ab.
44.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
45.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
46.	(hui or hui1 or hui2 or hui3).ti,ab.

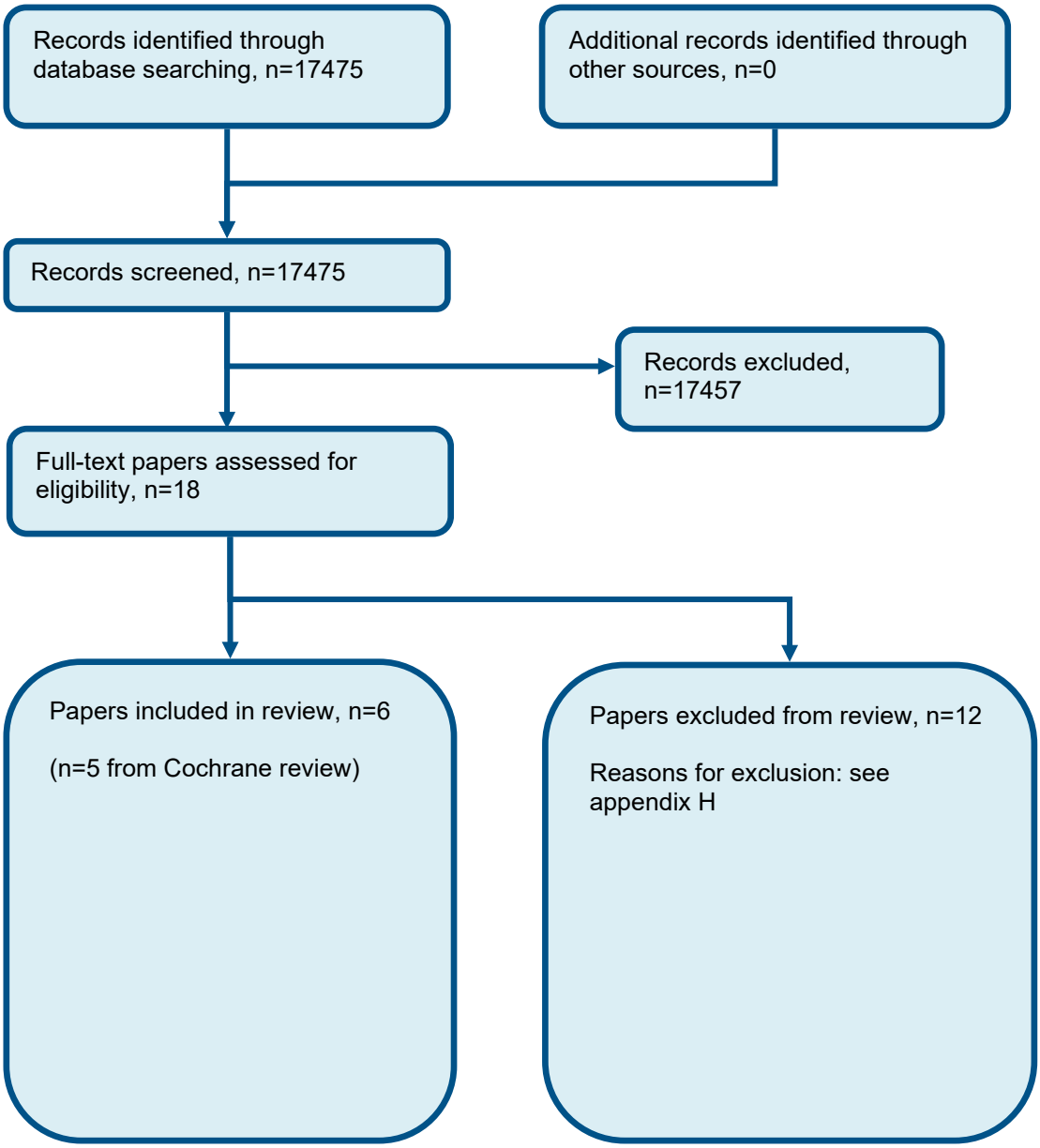
47.	(health* year* equivalent* or hye or hyes).ti,ab.
48.	discrete choice*.ti,ab.
49.	rosser.ti,ab.
50.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
51.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
52.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
53.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
54.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
55.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
56.	or/35-55
57.	20 and (34 or 56)
58.	limit 57 to English language

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Tinnitus EXPLODE ALL TREES
#2.	(tinnit*)
#3.	#1 OR #2

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of betahistine



Appendix D: Clinical evidence tables

Study	BEMED trial: Adrion 2016[1]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=147)
Countries and setting	Conducted in Germany; Setting: Outpatient dizziness services in the neurology department or the ear, nose, and throat department of 14 German university hospitals.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults with Meniere's disease
Subgroup analysis within study	Stratified then randomised: Stratified by study site
Inclusion criteria	Patients aged 18-80 years were eligible for enrolment if they presented with two or more definitive spontaneous episodes of vertigo of at least 20 minutes' duration, had audiometrically documented hearing loss on at least one occasion, and tinnitus or aural fullness in the treated ear, excluding other possible causes of vertigo. These factors made up a diagnosis of definite unilateral or bilateral Meniere's disease, fulfilling the criteria of the 1995 American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) guideline. Furthermore, patients had to be in an active phase of the disease, with at least two vertigo attacks per month in at least three consecutive months before enrolment.

Exclusion criteria	Exclusion criteria were diagnosis of other central or peripheral vestibular disorders such as vestibular migraine, benign paroxysmal positioning vertigo, paroxysmal brainstem attacks, as well as phobic postural vertigo. Patients were excluded if they had known contraindications or sensitivity to betahistine, such as bronchial asthma, pheochromocytoma, treatment with other antihistaminic drugs, ulcer of the stomach or duodenum, or severe dysfunction of liver or kidney. Safety related exclusion criteria were severe coronary heart disease or heart failure, persistent uncontrolled hypertension with systolic blood pressure higher than 180 mm Hg or diastolic blood pressure higher than 110 mm Hg, life expectancy less than 12 months, other serious illness, or a complex disease that might confound treatment assessment. General exclusion criteria were participation in another trial with an investigational drug or device within the past 30 days, previous participation in the present study, or planned participation in another trial. Pregnant and breastfeeding women and women contemplating pregnancy during the trial were excluded from enrolment. Female patients of childbearing potential were only included if they had a negative serum pregnancy test within seven days before initiation of treatment and were willing to practice acceptable methods of birth control during treatment and for three months after treatment.
Recruitment/selection of patients	A total of 1450 patients were screened for eligibility at 17 outpatient sites. Patients were enrolled in the study from 31 March 2008 (first patient, first visit) to 5 November 2013 (last patient, last visit), including a three month follow-up.
Age, gender and ethnicity	Age - Mean (SD): Placebo - 54.5 (12.8), Betahistine - 56.1 (11.1). Gender (M:F): 74:73. Ethnicity: 97% white
Further population details	1. People with learning disability or cognitive impairment: Not stated / Unclear (Not reported). 2. Profoundly deaf: Not stated / Unclear (Not reported).
Extra comments	
Indirectness of population	No indirectness: Note: not all participants necessarily had tinnitus as study population was Meniere's disease. However, as that was specified as a stratum of interest in this question, it is not considered indirect.

Interventions	(n=73) Intervention 1: Betahistine. 24mg twice per day. Betahistine dihydrochloride tablets were over-encapsulated with mannitol and aerosil as filling material. Capsules containing the active ingredient were refilled from original pharmacy packaging into vials under sterile conditions and relabelled by the pharmacy of the university hospital of the University of Heidelberg. Patients were instructed to take six capsules per day (two capsules in the morning, two at noon, and two in the evening). Patients took one betahistine capsule and one placebo capsule in the morning; two placebo capsules at noon; and one betahistine capsule together with one placebo capsule in the evening. . Duration 9 months. Concurrent medication/care: There were no disallowed concomitant drugs used during the study except for antihistaminic drugs, because the authors aimed to assess the efficacy of the assigned prophylactic treatment irrespective of rescue medication use by measuring efficacy conditional on real life adherence. Hence, rescue medication for managing of acute vertigo related symptoms such as vomiting or nausea could also be prescribed, because a possible effect on the occurrence of vertigo attacks is unknown.. Indirectness: No indirectness Comments: This study had two betahistine arms. Only the "low dose" arm has been extracted for this review as the "high dose" arm uses doses that are above the maximum licensed dose in the UK. (n=74) Intervention 2: Control group - Placebo. An identically appearing capsule filled with mannitol and aerosil but not containing any active ingredient was administered as placebo.. Duration 9 months. Concurrent medication/care: There were no disallowed concomitant drugs used during the study except for antihistaminic drugs, because the authors aimed to assess the efficacy of the assigned prophylactic treatment irrespective of rescue medication use by measuring efficacy conditional on real life adherence. Hence, rescue medication for managing of acute vertigo related symptoms such as vomiting or nausea could also be prescribed, because a possible effect on the occurrence of vertigo attacks is unknown. Indirectness: No indirectness
Funding	Academic or government funding (German Federal Ministry of Education and Research, German Centre for Vertigo and Balance Disorders)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BETAHISTINE versus PLACEBO	

Protocol outcome 1: Quality of life - Actual outcome for Adults with Meniere's disease: Change in quality of life (Mini-Tinnitus Questionnaire (Mini-TQ)) at 9 months; Group 1: mean -0.113 (SD 0.422599); n=70, Group 2: mean -0.121 (SD 0.441581); n=72; Mini Tinnitus Questionnaire (mini-QT) unclear Top=High is poor outcome; Comments: Note: data taken from Web Appendix 2 (complete case analyses) as these data were not transformed and therefore SDs could be calculated from the confidence intervals provided. Imputation undertaken by study authors as missing data, but methods unclear. Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: MiniTQ: placebo, mean (SD) - 0.765 (0.564), betahistine, mean (SD) - 0.807 (0.531); Group 1 Number missing: 19, Reason: Not reported; Group 2 Number missing: 16, Reason: Not reported	
Protocol outcomes not reported by the study	Tinnitus loudness; Tinnitus distress; Tinnitus annoyance; Depression; Anxiety ; Anxiety and depression; Sleep; Severity; Adverse events

Study (subsidiary papers)	**Wegner 2018[23] (Çekkayan 1996[3], Kay 1981[7], Ma 2006[9], Mashali 2016[12], Maqbool 2010[11])**
Study type	Systematic Review
Number of studies (number of participants)	5 (n=303 (or 305 - unclear))
Countries and setting	Conducted in Multiple countries; Setting: Four studies were conducted in otorhinolaryngology departments within hospitals (Cekkayan 1996; Ma 2006; Maqbool 2010; Mashali 2016). Kay 1981 did not mention the study setting in his article, but the author was an otorhinolaryngologist. All studies were single-centre (Cekkayan 1996;Kay 1981;Ma 2006;Maqbool 2010; Mashali 2016).
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 1 week - 3 months
Method of assessment of guideline condition	Systematic review: method of assessment mixed

Stratum	All ages, without Meniere's disease: Studies with > 50% participants with Meniere's Disease were excluded. Studies with < 50% of participants with Meniere's Disease were included but downgraded for indirectness.
Subgroup analysis within study	Sys review – pre-specified in protocol: The authors planned to perform the following subgroup analyses, but were not able to do so due to insufficient data: • age (children < 16 or 18 years and adults ≥ 16 or 18 years); • duration of tinnitus (acute ≤ 3 months and chronic > 3 months); • dose of betahistine administered (minimum daily dose of 8 mg to a maximum of 148 mg); • additional interventions (betahistine with and without an additional intervention).
Inclusion criteria	Types of studies: RCTs, including cluster randomised, and cross-over (if data from before the cross-over could be extracted). No restrictions on language, year of publication or publication status. Type of participants: Patients of any age with acute or chronic subjective idiopathic tinnitus. Participants who had received betahistine previously were eligible for inclusion. Types of interventions: all courses of betahistine, regardless of dose regimens or formulations and for any duration of treatment, compared with placebo, no intervention or education and information only.
Exclusion criteria	Types of studies: quasi-RCTs Types of participants: Patients with tinnitus as part of Meniere's disease were not considered to have idiopathic tinnitus, because tinnitus is one of the defining features of the diagnosis. Therefore, the authors excluded studies that included a majority (more than 50%) of patients with Meniere's disease.
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Range of means: 40 years to 50 years. Gender (M:F): Not reported overall. Ethnicity: Not reported
Further population details	1. People with learning disability or cognitive impairment: Not stated / Unclear (Not reported). 2. Profoundly deaf: Not stated / Unclear (Not reported).

Extra comments	Three studies recruited adult participants (18 years or over) according to their eligibility criteria (Ma 2006; Maqbool 2010; Mashali 2016). The criteria for inclusion or exclusion varied between studies. Kay 1981 excluded patients with cardiovascular risk based on a clinical history and electrocardiographic examination, because one group of participants received mexiletine in their trial. Likewise, Mashali 2016 excluded patients with severe heart disease and medication that interferes with carbamazepine, because one group of participants received carbamazepine in their trial. Maqbool 2010 only included male military personnel with noise-induced hearing loss. The participant groups in these three studies may not fully represent the tinnitus population (Kay 1981; Maqbool 2010; Mashali 2016).
Indirectness of population	No indirectness: Review population not indirect. However, some of the included studies were downgraded by the authors for indirectness of the population (inclusion of patients with Meniere's Disease, inclusion of only male participants/military personnel with noise-induced hearing loss)
Interventions	(n=92) Intervention 1: Betahistine without concurrent medication. Four studies evaluated the effect of betahistine without concurrent medication. Different salts of betahistine were used. Cekkayan 1996 and Maqbool 2010 evaluated the effect of betahistine hydrochloride, and Kay 1981 and Mashali 2016 evaluated betahistine not otherwise specified. The daily dosage varied from 16 mg daily to 48 mg daily. One study prescribed 8 mg twice daily initially followed by 8 mg three times daily for 28 days (Kay 1981). A third study prescribed 16 mg three times daily for two months (Maqbool 2010) and a fourth study 8 mg twice daily for 12 weeks (Mashali 2016). Cekkayan 1996 did not report dosage or frequency. . Duration 28 days - 3 months. Concurrent medication/care: None reported. Indirectness: No indirectness Comments: Number randomised is an estimate, not always reported in included studies (n=79) Intervention 2: Control group – Placebo without concurrent medication. Four of the studies included a placebo arm without concurrent medication. Details of the placebo were not specified in three of the included studies. In the other study, a multivitamin was used as a placebo. Duration 28 days - 3 months. Concurrent medication/care: None reported. Indirectness: No indirectness Comments: Number randomised is an estimate as not always reported in included studies (n=30) Intervention 3: Betahistine with concurrent medication. One study (Ma 2006) evaluated betahistine with concurrent medication. Betahistine mesilate was prescribed 6 mg three times daily

	for one week (Ma 2006).. Duration 1 week. Concurrent medication/care: Both treatment arms received flunarizine hydrochloride, 5 mg daily for one week. Indirectness: No indirectness (n=30) Intervention 4: Control group – Placebo with concurrent medication. One study (Ma 2006) used a placebo with concurrent medication. Vitamin B6 was used as the placebo. . Duration 1 week. Concurrent medication/care: Both treatment arms received flunarizine hydrochloride, 5 mg daily for one week.. Indirectness: No indirectness
Funding	Academic or government funding (National Institute for Health Research, UK)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BETAHISTINE (WITHOUT CONCURRENT MEDICATION) versus PLACEBO (WITHOUT CONCURRENT MEDICATION)

Protocol outcome 1: Tinnitus loudness
- Actual outcome for All ages, without Meniere's disease: Tinnitus loudness (VAS) at 1 month; MD; -0.16 (95%CI -1.01 to 0.7) Visual analogue scale unclear Top=High is poor outcome, Comments: One study used a 0-10 scale and the other did not report the upper limit of the scale.;
Risk of bias: All domain - Unclear, Selection - Unclear, Blinding - Unclear, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Unclear, Crossover - Low, Comments - Cochrane's ROB assessment extracted here; Indirectness of outcome: Serious indirectness, Comments: in one study a patient with Ménière's disease was included and in the other studies only male participants/military personnel with noise-induced hearing loss were included
; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for All ages, without Meniere's disease: Tinnitus loudness (VAS) at 2 months; MD; -0.39 (95%CI -1.37 to 0.6) Visual analogue scale 0-10 Top=High is poor outcome;
Risk of bias: All domain - Unclear, Selection - Unclear, Blinding - Unclear, Incomplete outcome data - Unclear, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Cochrane's ROB assessment extracted here; Indirectness of outcome: Serious indirectness, Comments: only male participants/military personnel with noise-induced hearing loss were included
; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for All ages, without Meniere's disease: Change in tinnitus loudness (VAS) at 28 days; MD; -0.43 (95%CI -1.2 to 0.34) Visual analogue scale Unclear Top=High is poor outcome;
Risk of bias: All domain - Unclear, Selection - Unclear, Blinding - Unclear, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Unclear, Crossover - Low, Comments - Cochrane's ROB assessment extracted here; Indirectness of outcome: Serious

indirectness, Comments: a patient with Ménière’s disease was included
; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Severity
- Actual outcome for All ages, without Meniere's disease: Change in Tinnitus Severity Index at 12 weeks; MD; 0.02 (95%CI -1.05 to 1.09) Tinnitus Severity Index 0 to 56 Top=High is poor outcome;
Risk of bias: All domain - Unclear, Selection - Unclear, Blinding - Unclear, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Comments - Cochrane's ROB assessment extracted here; Indirectness of outcome: No indirectness, Comments:
; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for All ages, without Meniere's disease: Tinnitus severity score at 3 months; MD; -0.52 (95%CI -1.34 to 0.3) Tinnitus Severity Scale 0 to 4 Top=High is poor outcome, Comments: A single-item five-point Likert scale: 0 = the tinnitus disappeared completely; 1 = great relief, but the complaint was still ongoing; 2 = relieved by 50%; 3 = relief was very small; 4 = no changes were noticed;
Risk of bias: All domain - Unclear, Selection - Unclear, Blinding - Unclear, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Comments - Cochrane's ROB assessment extracted here; Indirectness of outcome: No indirectness, Comments:
; Group 1 Number missing; Group 2 Number missing:

Protocol outcome 3: Adverse events
- Actual outcome for All ages, without Meniere's disease: Significant adverse effects at 28 days; Group 1: 0/92, Group 2: 0/92
Risk of bias: All domain - Unclear, Selection - Unclear, Blinding - Unclear, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Unclear, Crossover - Low, Comments - Cochrane's ROB assessment extracted here; Indirectness of outcome: Serious indirectness, Comments: A patient with Meniere's Disease was included
; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for All ages, without Meniere's disease: Significant adverse effects at 3 months; Group 1: 0/92, Group 2: 0/79
Risk of bias: All domain - Unclear, Selection - Unclear, Blinding - Unclear, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Comments - Cochrane's ROB assessment extracted here; Indirectness of outcome: No indirectness, Comments:
; Group 1 Number missing; Group 2 Number missing:
- Actual outcome for All ages, without Meniere's disease: Other adverse effects at 28 days; RR; 3.50 (95%CI 0.17 to 70.94);
Risk of bias: All domain - Unclear, Selection - Unclear, Blinding - Unclear, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Unclear, Crossover - Low, Comments - Cochrane's ROB assessment extracted here; Indirectness of outcome: Serious indirectness, Comments: A patient with Meniere's Disease was included
; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for All ages, without Meniere's disease: Other adverse effects at 3 months; Group 1: 0/92, Group 2: 0/79

Risk of bias: All domain - Unclear, Selection - Unclear, Blinding - Unclear, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Comments - Cochrane's ROB assessment extracted here; Indirectness of outcome: No indirectness, Comments:
; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BETAHISTINE (WITH CONCURRENT MEDICATION) versus PLACEBO (WITH CONCURRENT MEDICATION)

Protocol outcome 1: Tinnitus loudness
- Actual outcome for All ages, without Meniere's disease: Change in tinnitus loudness match at 1 week; MD; -0.10 (95%CI -0.5 to 0.3) See comments 0 to 5 Top=High is poor outcome, Comments: 1 = loudness decreased to 0 dB; 2 = loudness reduced by 15 dB or more; 3 = loudness reduced by 5 dB or more and less than 15 dB; 4 = loudness reduced by less than 5 dB or increased by less than 5 dB; 5 = loudness increased by 5 dB or more;
Risk of bias: All domain - Unclear, Selection - Unclear, Blinding - Unclear, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Cochrane's ROB assessment extracted here; Indirectness of outcome: No indirectness, Comments:
; Group 1 Number missing; Group 2 Number missing:

Protocol outcome 2: Adverse events
- Actual outcome for All ages, without Meniere's disease: Significant adverse effects at 1 week; RR; 3.10 (95%CI 0.13 to 73.14);
Risk of bias: All domain - Unclear, Selection - Unclear, Blinding - Unclear, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Cochrane's ROB assessment extracted here; Indirectness of outcome: No indirectness, Comments:
; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for All ages, without Meniere's disease: Other adverse effects at 1 week; RR; 0.44 (95%CI 0.13 to 1.55);
Risk of bias: All domain - Unclear, Selection - Unclear, Blinding - Unclear, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Cochrane's ROB assessment extracted here; Indirectness of outcome: No indirectness, Comments:
; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	Tinnitus distress; Tinnitus annoyance; Depression ; Anxiety ; Anxiety and depression; Sleep; Quality of life

Appendix E: Forest plots

E.1 People with Tinnitus (without Meniere's Disease)

E.1.1 Betahistine versus placebo (without concurrent medication)

Figure 2: Tinnitus loudness, VAS at 1 month; scale range unclear

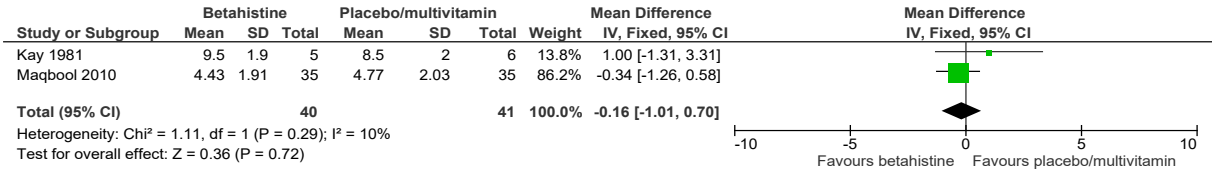


Figure 3: Tinnitus loudness, VAS at 2 months; scale range 0-10

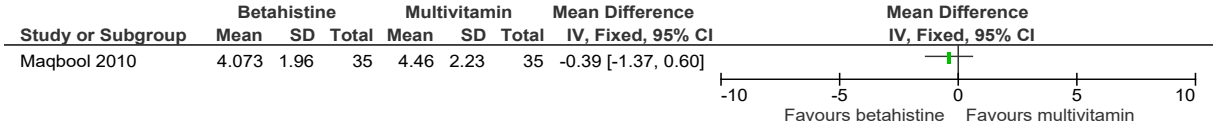


Figure 4: Change in tinnitus loudness, VAS at 28 days; scale range unclear

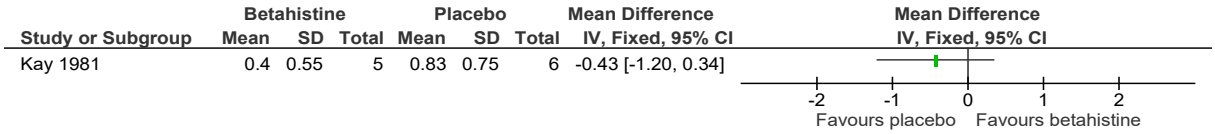


Figure 5: Change in Tinnitus Severity Index at 12 weeks; scale range 0 to 56

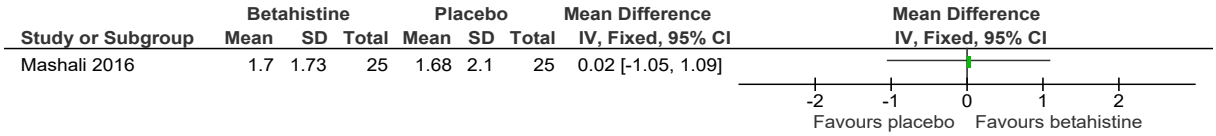


Figure 6: Tinnitus Severity Score/Scale at 3 months; scale range 0 to 4

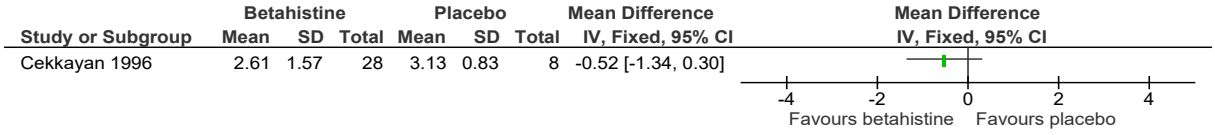


Figure 7: Significant adverse effects at 28 days

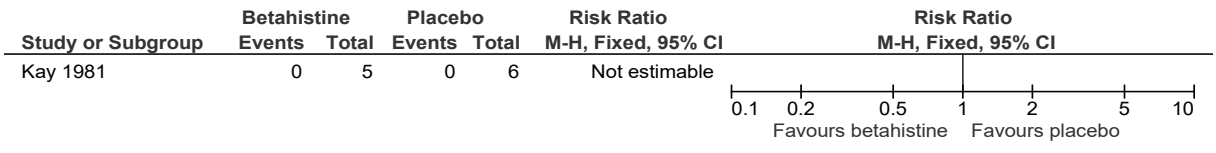


Figure 8: Significant adverse effects at 3 months

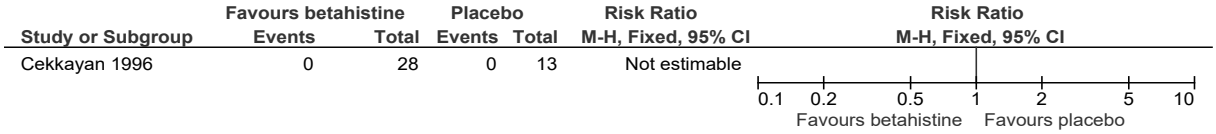


Figure 9: Other adverse effects at 28 days

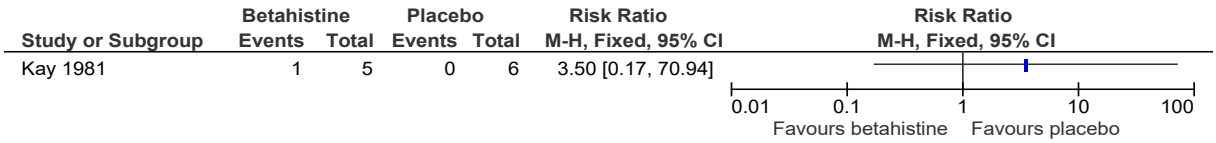
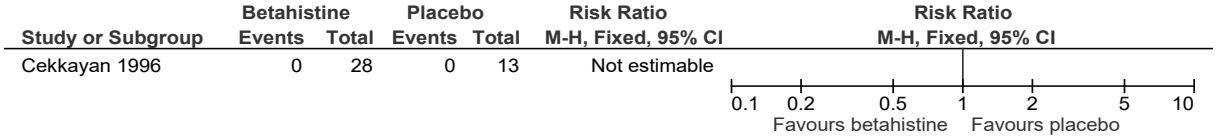


Figure 10: Other adverse effects at 3 months



E.1.2 Betahistine versus placebo (with concurrent medication)

Figure 11: Change in tinnitus loudness match at 1 week; scale range 0 to 5

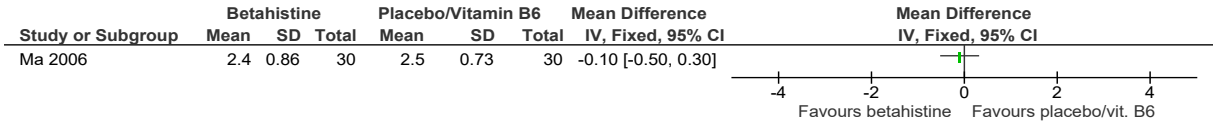


Figure 12: Significant adverse effects at 1 week

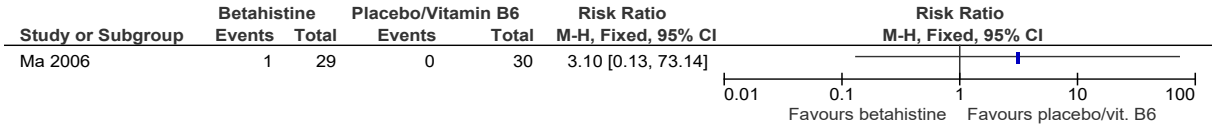
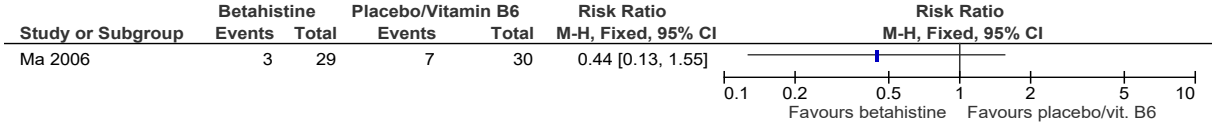


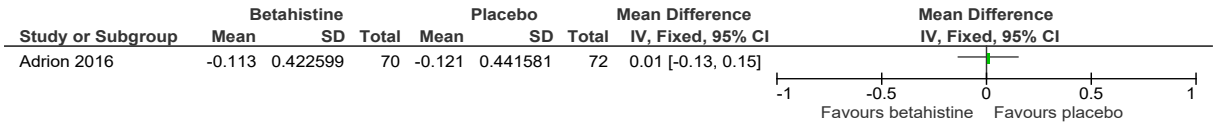
Figure 13: Other adverse effects at 1 week



E.2 People with Meniere's Disease

E.2.1 Betahistine versus placebo (without concurrent medicine)

Figure 14: Change in quality life, Mini-Tinnitus Questionnaire at 9 months, scale range unclear



Appendix F: GRADE tables

Table 9: Clinical evidence profile: Betahistine (without concurrent medication) versus placebo in people with tinnitus (without Meniere's Disease)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Betahistine (without concurrent medication)	Placebo	Relative (95% CI)	Absolute		
Tinnitus loudness (follow-up 1 months; measured with: visual analogue scale; range of scores: 0-10; Better indicated by lower values)												
2	randomised trials	serious[1]	serious[1]	serious[1]	serious[1]	none	40	41	-	MD 0.16 lower (1.01 lower to 0.7 higher)	⊕OOO VERY LOW	IMPORTANT
Tinnitus loudness (follow-up 2 months; measured with: visual analogue scale; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[2]	no serious inconsistency	serious[2]	serious[2]	none	35	35	-	MD 0.39 lower (1.37 lower to 0.6 higher)	⊕OOO VERY LOW	IMPORTANT
Change in tinnitus loudness (follow-up 28 days; measured with: visual analogue scale; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[3]	no serious inconsistency	serious[3]	serious[3]	none	5	6	-	MD 0.43 lower (1.2 lower to 0.34 higher)	⊕OOO VERY LOW	IMPORTANT
Change in tinnitus severity (follow-up 12 weeks; measured with: Tinnitus Severity Index; range of scores: 0-56; Better indicated by lower values)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	25	25	-	MD 0.02 higher (1.05 lower to 1.09 higher)	⊕⊕⊕O MODERATE	CRITICAL
Tinnitus severity (follow-up 3 months; measured with: tinnitus severity score/scale; range of scores: 0-4; Better indicated by lower values)												

1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[5]	none	28	8	-	MD 0.52 lower (1.34 lower to 0.3 higher)	⊕⊕OO LOW	CRITICAL
Significant adverse effects (follow-up 28 days)												
1	randomised trials	serious[3]	no serious inconsistency	serious[3]	very serious[3]	none	0/5 (0%)	0/6 (0%)[6]	-	-	⊕OOO VERY LOW	IMPORTANT
Significant adverse effects (follow-up 3 months)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/28 (0%)	0/13 (0%)[6]	-	-	⊕⊕⊕O MODERATE	IMPORTANT
Other adverse effects (follow-up 28 days)												
1	randomised trials	serious[3]	no serious inconsistency	serious[3]	serious[3]	none	1/5 (20%)	0/6 (0%)	RR 3.5 (0.17 to 70.94)	-[7]	⊕OOO VERY LOW	IMPORTANT
Other adverse effects (follow-up 3 months)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/28 (0%)	0/13 (0%)[6]	-	-	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded one level due to an unclear overall risk of bias in both studies; downgraded one level due to inconsistency (one study has a slight preference for betahistine and the other for placebo); downgraded one level due to indirectness (in one study a patient with Meniere's disease was included and in the other studies only male participants/military personnel with noise-induced hearing loss were included); downgraded one level due to imprecision.
[2] Downgraded one level due to an unclear overall risk of bias, downgraded one level due to indirectness (only male participants/ military personnel with noise-induced hearing loss were included); downgraded one level due to imprecision.
[3] Downgraded one level due to an unclear overall risk of bias, downgraded one level due to indirectness (a patient with Meniere's disease was included); downgraded one level due to imprecision.
[4] Downgraded one level due to an unclear overall risk of bias.
[5] Downgraded one level due to an unclear overall risk of bias; downgraded one level due to imprecision.
[6] Zero events in both arms.
[7] Due to zero events in the control arm, absolute effect could not be calculated.

Table 10: Clinical evidence profile: Betahistine (with concurrent medication) versus placebo in people with tinnitus (without Meniere's Disease)

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Betahistine (with concurrent medication)	Placebo	Relative (95% CI)	Absolute		
Change in tinnitus loudness match (follow-up 1 weeks; range of scores: 0-5; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30	30	-	MD 0.10 lower (0.5 lower to 0.3 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Significant adverse effects (follow-up 1 weeks)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[2]	none	1/29 (3.4%)	0/30 (0%)	RR 3.10 (0.13 to 73.14)	-[3]	⊕⊕OO LOW	IMPORTANT
Other adverse effects (follow-up 1 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	3/29 (10.3%)	7/21 (33.3%)	RR 0.44 (0.13 to 1.55)	187 fewer per 1000 (from 290 fewer to 183 more)	⊕⊕⊕O MODERATE	IMPORTANT

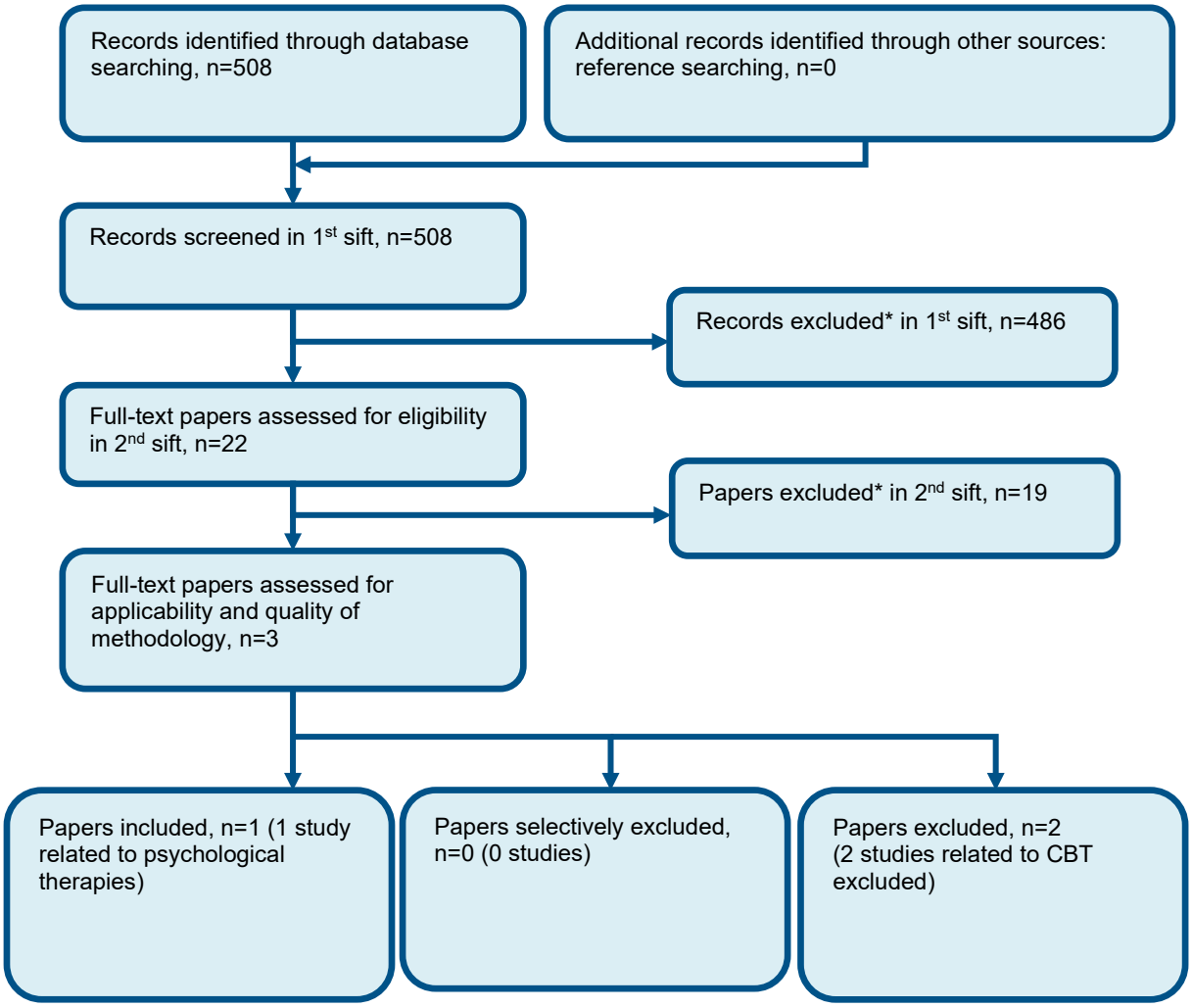
[1] Downgraded one level due to an unclear overall risk of bias.
[2] Downgraded one level due to an unclear overall risk of bias; downgraded one level due to imprecision.
[3] Due to zero events in the control arm, absolute effect could not be calculated.

Table 11: Clinical evidence profile: Betahistine versus placebo in people with Meniere's Disease

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Betahistine**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Quality of life (follow-up 9 months; measured with: Mini Tinnitus Questionnaire; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	70	72	-	MD 0.01 higher (0.13 lower to 0.15 higher)	⊕⊕⊕⊕ HIGH	CRITICAL

Appendix G: Health economic evidence selection

Table 12: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H: Excluded studies

H.1 Excluded clinical studies

Table 13: Studies excluded from the clinical review

Study	Exclusion reason
Albu 2015[2]	Inappropriate comparison (IT dexamethasone and placebo versus high dosage betahistine and IT saline)
Elia 1966[4]	No relevant extractable outcomes
Kluyskens 1990[8]	Not in English
Mahendru 2013[10]	Incorrect study design (conference abstract)
Okamato 1968[15]	Not in English
Oosterveld 1984[16]	Not review population (Meniere's disease and vertigo)
Pilling 1982[17]	Incorrect interventions (modified gas-liquid chromatographic assay to monitor plasma mexiletine)
Ricci 1987[18]	Not in English
Salami 1984[19]	Not in English
Schmidt 1992[20]	No relevant extractable outcomes
Singarelli 1979[21]	Not in English
Sönmez 2013[22]	Inappropriate study design (alternate randomisation)

H.2 Excluded health economic studies

None.