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**Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)**
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# Is betahistine effective for Ménière's disease?

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## Abstract

**PROBLEM**
Meniere's disease is an inner ear disorder characterized by episodes of spontaneous vertigo, fluctuating hearing loss and tinnitus. Betahistine has been used to reduce intensity and frecuency of vertigo attacks, but there is controversy regarding its effectiveness.

**METHODS**
To answer this question we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others. We extracted data from the systematic reviews, reanalyzed data of primary studies, conducted a meta-analysis and generated a summary of findings table using the GRADE approach.

**RESULTS AND CONCLUSIONS**
We identified four systematic reviews including 12 trials overall. We concluded betahistine might reduce the number of attacks, vertigo intensity and lead to a symptomatic improvement according to global judgement in patients with Meniere's disease, but the certainty of evidence is low. On the other hand, it probably does not have significant adverse effects.

## Problem

Ménière's disease is an inner ear disorder characterized by episodes of spontaneous vertigo, fluctuating hearing loss and tinnitus. One of the most used diagnostic criteria, although not universally accepted, includes the presence of two vertigo episodes with a duration grater than 20 minutes, audiometric confirmation of sensorineural hearing loss, plus tinnitus or aural fullness perception [1].
Ménière's disease is caused by an increase in endolymphatic pressure in the inner ear, from unknown etiology. This leads to recurrent and frequent vertigo attacks with substantive impact on quality of life, followed by periods of remission that can last several months [2].
Betahistine has long been used to reduce intensity and frecuency of vertigo attacks and tinnitus, since it would delay progression of hearing loss in Ménière's disease. The alleged mechanism is endolymph pressure reduction secondary to microcirculation improvement at the stria vascularis of the cochlea. Another proposed mechanism relates to vestibular nucleus activity inhibition. However, there is controversy regarding its effectiveness.

## Methods

To answer the question, we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others, to identify systematic reviews and their included primary studies. We extracted data from the identified reviews and reanalyzed data from primary studies included in those reviews. With this information, we generated a structured summary denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos) using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies when it is possible, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

**Key messages**

- Betahistine might reduce the number of vertigo attacks, intensity of vertigo, and lead to symptomatic improvement according to global judgement of patients with Ménière's disease, but the certainty of the evidence is low.
- Betahistine probably does not have important adverse effects.

### About the body of evidence for this question

| | |
|---|---|
| What is the evidence. See evidence matrix in Epistemonikos later | We found four systematic reviews [3],[4],[5],[6] including 12 primary studies relevant for our question [7],[8],[9],[10],[11],[12],[13],[14],[15],[16],[17],[18], all of them randomized controlled trials. |
| What types of patients were included* | Some trials did not use the American Academy of Otolaryngology –Head and Neck Surgery guidelines' criteria for Ménière's disease [1]. In consequence, some systematic reviews did not include them into their analysis. In order to present direct evidence, these are presented in this table, but were not used to estimate the effect of benefits in the summary of findings table.<br>Six trials specified the inclusion of patients with clinical Ménière's disease [8],[10],[11],[12],[14],[17].<br>One of the trials included patients with progressive episodic vertigo [9], two included patients with two or three months of peripheral vertigo [7],[13] and one with recurrent vertigo defined as two or more vertigo attacks in the last month [15]. Two trials did not specify the inclusion criteria [16],[18]. |
| What types of interventions were included* | All trials compared betahistine against placebo.<br>Two trials used 4 mg six times per day [11],[16]. Two used 8 mg every 8 hours [12],[14], two used 16 mg every 8 hours [9],[15] and one trial two times per day [17]. Other trials used 12 mg every 8 hours [7], 18 mg two times per day [8], 24 mg every 8 hours [18] and every 12 hours [10]. One trial allowed a dose up to 48 mg per day [13]. |
| What types of outcomes were measured | Outcomes, according to how they were grouped in the identified systematic reviews were:<br>• Number, intensity and duration of acute attacks of vertigo<br>• Hearing<br>• Severity of tinnitus<br>• Perception of aural fullness<br>• Functional impairment and disability<br>• Overall wellbeing and quality of life<br>• Side effects of betahistine<br>• Vestibular function tested with objective tests<br>• Opinion on the response of vertigo symptoms<br>• Overall clinical evaluation of the change in patient`s condition<br>• Patients dropping out from study.<br>The mean follow-up was 8.25 weeks, with a range between 2 and 12 weeks. |

* The information about primary studies is extracted from the systematic reviews identified, unless otherwise specified.

**Summary of findings**

The information about the effects of betahistine on Ménière's disease is based on 12 randomized trials. Only six trials included patients with clinical disease [8],[10],[11],[12],[14],[17] including 327 patients. Only one trial reported the number of vertigo attacks and intensity of symptoms [17] and three trials measured improvement according to global judgement of patients. Adverse effects were assessed in seven trials [7],[8],[10],[11],[13],[14],[17].

- Betahistine might reduce the number of vertigo attacks in patients with Ménière's disease. The certainty of the evidence is low.
- Betahistine might reduce the intensity of vertigo in patients with Ménière's disease. The certainty of the evidence is low.
- Betahistine might lead to symptomatic improvement according to global judgement of patients with Ménière's disease. The certainty of the evidence is low.
- Betahistine probably does not have important adverse effects in patients with Ménière's disease. The certainty of the evidence is moderate.

| Betahistine for Ménière's disease | | | | |
|---|---|---|---|---|
| Patients | Ménière disease | | | |
| Intervention | Betahistine | | | |
| Comparison | placebo | | | |
| Outcomes | Absolute effect* | | Relative effect (95% CI) | Certainty of the evidence (GRADE) |
| | WITHOUT betahistine | WITH betahistine | | |
| | Difference: patients per 1000 | | | |
| Number of vertigo attacks At 3 months | 5.03 crisis | 2.29 crisis | - | ⊕⊕◯◯[1,2] Low |
| | MD: 2.74 less crisis (Margin of error: 0.61 to 4.87 less) | | | |
| Vertigo intensity At 3 months ** | 1.26 | 0.51 | - | ⊕⊕◯◯[1,2] Low |
| | MD: 0.55 less (Margin of error: 0.18 to 0.92 less) | | | |
| Symptomatic improvement according to global judgement *** | 333 per 1000 | 566 per 1000 | RR 7 (1.17 to 2.46) | ⊕⊕◯◯[1,3] Low |
| | Difference: 233 patients more (Margin of error: 57 to 487 more) | | | |
| Adverse effects | 146 per 1000 | 153 per 1000 | RR 1.05 (0.72 to 1.55) | ⊕⊕⊕◯[4] Moderate |
| | Difference:7 patients more per 1000 (Margin of error: from: 41 less to 80 more) | | | |

RR: Risk ratio.
MD: Mean difference.
Margin of error: 95% confidence interval (CI).
GRADE: evidence grades of the GRADE Working Group (see later in this article)

* The risk **WITHOUT betahistine** is based on the risk in the control group of the trials. The risk **WITH betahistine** (and its margin of error) is calculated from relative effect (and its margin of error)
** Four-point scale (0 = absent, 1 = mild, 2 = severe, 3 = disabling)
*** Considers global symptomatic improvement of vertigo reported by patient in terms of intensity, frequency and duration.

[1] The certainty of evidence was downgraded for risk of bias, since the only trial included for the analysis has high risk of selective reporting and the blinding of outcome assessment is not clear.
[2] The certainty of evidence was downgraded for imprecision, since the confidence interval includes the chance of little or null effect in clinical terms.
[3] The certainty of evidence was downgraded because it was considered indirect evidence for the outcome, since non-validated outcome measures were used.
[4] The certainty of evidence was downgraded for imprecision, since the confidence interval could support or not the intervention.

**About the certainty of the evidence (GRADE)***

⊕⊕⊕⊕

**High:** This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯

**Moderate:** This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate

⊕⊕◯◯

**Low:** This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯

**Very low:** This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.

† Substantially different = a large enough difference that it might affect a decision.

## Other considerations for decision-making

### To whom this evidence does and does not apply

- The results of this summary apply to patients with Ménière's disease who have symptoms of vertigo.
- In this summary we used the trials including patients who met the clinical definition of Ménière's disease; however, the reviews assessing a broader set of patients with vertigo, arrived to similar conclusions, so it is reasonable to extrapolate the results to these patients.

### About the outcomes included in this summary

- The results of this summary apply to patients with Ménière's disease who have symptoms of vertigo.
- In this summary we used the trials including patients who met the clinical definition of Ménière's disease; however, the reviews assessing a broader set of patients with vertigo, arrived to similar conclusions, so it is reasonable to extrapolate the results to these patients.

### Balance between benefits and risks, and certainty of the evidence

- Since the certainty of the evidence is low for reducing the number of vertigo attacks, vertigo intensity and global symptomatic improvement, it is difficult to make a balance between risk and benefits for betahistine in patients with Ménière's disease. On the other hand, it probably does not have adverse effects.

### Resource considerations

- Betahistine has a relatively high cost. However, it is difficult to make a balance between costs and benefits, due to the uncertainty about the latter.

### What would patients and their doctors think about this intervention

- Variability in decision-making for this intervention can be expected. Patients who put more emphasis on an uncertain benefit may be inclined to use it. Those who put more value on the certainty of the evidence or costs, are likely to lean against its use.
- One factor to consider among physicians is that during their clinical experience they have historically used betahistine and there is heterogeneity in existing recommendations in clinical practice guidelines. This is likely to contribute to even greater variability in decision-making.

### Differences between this summary and other sources

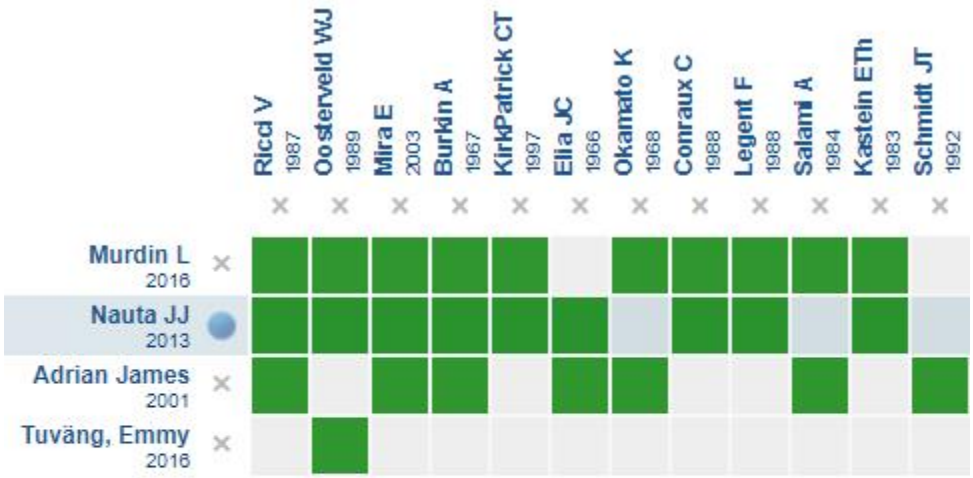
- The conclusions of this summary are consistent with two of the four included systematic reviews [4],[5], and partially concordant with the others.
- These results are also consistent with clinical practice guidelines on Ménière's disease from Spain [19], Mexico [20] and France [21], and partially concordant with Philippine`s guidelines, which strongly recomend its use [22]. American AAO-NHS guidelines are still in process.

### Could this evidence change in the future?

- The probability of the conclusions of this summary changing with future trials is high because of the existing uncertainty about the benefits of betahistine.
- We identified at least two trials, not included in systematic reviews, that could help to clarify the evidence regarding this topic [23],[24].
- We searched for ongoing studies on the World Health Organization International Clinical Trials Registry Platform and found at least one unpublished trial on this topic [25].

### How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.




An evidence matrix is a table that compares systematic reviews that answer the same question.
Rows represent systematic reviews, and columns show primary studies.
The boxes in green correspond to studies included in the respective revisions.
The system automatically detects new systematic reviews including any of the primary studies in the matrix, which will be added if they actually answer the same question.

Follow the link to access the **interactive version:** Betahistine for Ménière's disease

## Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier.

After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

This article is part of the Epistemonikos Evidence Synthesis project. It is elaborated with a pre-established methodology, following rigorous methodological standards and internal peer review process. Each of these articles corresponds to a summary, denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence for a specific question, with a friendly format to clinical professionals. Its main resources are based on the evidence matrix of Epistemonikos and analysis of results using GRADE methodology. Further details of the methods for developing this FRISBEE are described here (http://dx.doi.org/10.5867/medwave.2014.06.5997)

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database (www.epistemonikos.org).

**Potential conflicts of interest**
The authors do not have relevant interests to declare.

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