Intratympanic gentamicin compared with placebo for Ménière´s disease

Fernanda de Amesti[1,2], Maria Jesus Santander[2,3], Matias Winter[2,3]

[1] *Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile*
[2] *Proyecto Epistemonikos, Santiago, Chile*
[3] *Departamento de Otorrinolaringología, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile*

*** Corresponding author** mwinterd@gmail.com

Citation de Amesti F., Santander M., Winter M. Intratympanic gentamicin compared with placebo for Ménière's disease *Medwave* 2022;22(02):e8695

Doi 10.5867/medwave.2022.02.8695

Submission date 12/08/2019
Acceptance date 22/01/2020
Publication date 22/03/2022

Origin This article is a product of the Evidence Synthesis Project of Epistemonikos Fundation, in collaboration with Medwave for its publication.

Type of review Not non-blind peers by the UC Evidence Center methodological team in collaboration with Epistemonikos Evidence Synthesis Project.

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

Key words Ménière, Gentamicin, Epistemonikos, GRADE.

Abstract

Introduction

Ménière's disease is a multifactorial disorder affecting the inner ear, characterized by episodes of spontaneous and recurrent vertigo, fluctuating hearing loss and tinnitus. Intratympanic gentamicin therapy has been used to reduce the intensity and frequency of attacks in intractable Ménière's disease, but it is associated with hearing loss. There is controversy regarding its efficacy and safety.

Methods

We searched in 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 13 systematic reviews that included 80 primary studies overall, of which three correspond to randomized trials. We concluded that intratympanic gentamicin may improve the control of vertigo, and result in little or no difference to tinnitus, but the certainty of the evidence is low. Furthermore, we are uncertain whether intratympanic gentamicin reduces hearing or the frequency of vertigo attacks as the certainty of the evidence has been assessed as very low.

Problem

Ménière's disease is a chronic, disabling and progressive illness, characterized by recurrent episodic spontaneous vertigo, hearing loss, aural fullness and tinnitus. The initial treatment consists of lifestyle modifications, including dietary sodium restriction, and medications such as diuretics and betahistine. However, it is estimated that 10% [1] of patients are refractory to the initial management, presenting at least one attack per month along with sensory hearing loss for six months or more [2]. Consequently, other more expensive and with a higher complication rate treatment alternatives, as surgical interventions, are considered.

Since there is no standard management for refractory Ménière's disease, multiple alternatives have been proposed, including the use of intratympanic aminoglycosides, specifically gentamicin, considered a minimally invasive therapy. Gentamicin acts at the inner ear level, producing partial or total ablation of the vestibular organ, mainly in vestibular hair cells, resulting in control of vertigo with less damage to the cochlear function [1]. However, there is no consensus on the protocol for intratympanic administration of gentamicin, nor clarity regarding its effectiveness and safety.

Key messages

- The use of intratympanic gentamicin may reduce the intensity of vertigo (the certainty of the evidence is low).
- The use of intratympanic gentamicin may make little or no difference in tinnitus (the certainty of the evidence is low).
- We are uncertain whether the use of intratympanic gentamicin reduces hearing loss or frequency of vertigo attacks (the certainty of the evidence is very low).
- No evidence was found evaluating adverse effects and quality of life.

About the body of evidence for this question

What is the evidence? See evidence matrix in Epistemonikos later	We found 13 systematic reviews [3], [4], [5], [6], [7], [8], [9], [10], [11], [12], [13], [14], [15], that included 80 primary studies [16], [17], [18], [19], [20], [21], [22], [23], [24], [25], [26], [27], [28], [29], [30], [31], [32], [33], [34], [35], [36], [37], [38], [39], [40], [41], [42], [43], [44], [45], [46], [47], [48], [49], [50], [51], [52], [53], [54], [55], [56], [57], [58], [59], [60], [61], [62], [63], [64], [65], [66], [67], [68], [69], [70], [71], [72], [73], [74], [75], [76], [77], [78], [79], [80], [81], [82], [83], [84], [85], [86], [87], [88], [89], [90], [91], [92], [93], [94], [95], three of which correspond to randomized trials [23], [73], [87]. This table and the summary in general are based on the randomized trials, as the observational studies did not increase the level of certainty of the evidence, nor added any additional relevant information.
What types of patients were included*	The diagnostic criteria used in the three trials [23], [73], [87], was obtained from a 1995 clinical guideline of the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) for the diagnosis of unilateral Ménière's disease. Two trials selected patients without previous surgical intervention [73], [87] and all of them included patients refractory to conservative management, defined as failure after six months [23], [87] or failure after treatment with betahistine [73] . One of the trials [73] included patients who presented a positive caloric response measured by electronystagmography.
What types of interventions were included*	Two of the trials used intratympanic gentamicin at 30 mg/ml with a weekly titration protocol [73], [87]. One trial used a dose of 0.4 ml [73] and the other one used four ml [87]. One of them installed a ventilation tube in the tympanic membrane four weeks prior to the start of treatment where gentamicin was injected [73], unlike the other trial that used tympanic puncture [87]. The remaining trial [23] used

Methods

We searched in 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.

	gentamicin at 40 mg/ml weekly without defining the volume. The cumulative dose differed between one [87] to four [23], [73]. All trials compared against placebo. One trial injected four ml of a buffer solution [87], another trial used 0.4 ml weekly for four weeks [73]. The remaining trial used 0.9% NaCl without specifying dose [23].
What types of outcomes were measured	The trials evaluated multiple outcomes, which were grouped by the systematic reviews as follows: Control of vertigo: measured as number of attacks per year and intensity of vertigo • Hearing loss or improvement • Tinnitus severity • Perception of aural fullness • Complications and adverse effects • Quality of life • Functionality scale The average follow-up of the studies was 17.7 months with a range between 6 and 28 months [23], [73], [87].

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

Summary of findings

The information on the effects of intratympanic gentamicin for intractable Ménière's disease is based on three randomized trials that included 60 patients [23], [73],[87].

One trial reported reduction of vertigo intensity (28 patients) [73] and three reported hearing loss (60 patients) [23], [73], [87]. No review allowed the extraction of data on vertigo attacks per year and tinnitus, therefore the information on these is presented as a narrative synthesis. None of the trials reported quality of life and adverse effects.

The summary of findings is the following:

- The use of intratympanic gentamicin may reduce intensity of vertigo (the certainty of the evidence is low).
- We are uncertain whether intratympanic gentamicin reduces hearing because the certainty of the evidence has been assessed as very low.
- We are uncertain whether intratympanic gentamicin reduces the frequency of attacks of vertigo per year, because the certainty of the evidence has been assessed as very low.
- Intratympanic gentamicin use may result in little or no difference in tinnitus (the certainty of the evidence is low).
- No studies were found that evaluated the quality of life outcome.
- No studies were found that evaluated the outcome of adverse effects.

Intratympanic gentamicin for *Ménière*'s disease

Patients *Ménière*'s disease
Intervention Intratympanic gentamicin
Comparison Placebo

Outcome	Absolute effect*		Certainty of evidence (GRADE)
	WITHOUT Intratympanic Gentamicin	**WITH Intratympanic Gentamicin**	
	Difference: patients per 1000		
Intensity of vertigo**	1.8 points	0.5 points	⊕⊕◯◯[1,2] Low
	MD: 1.3 less (Margin of error: 0.66 to 1.94 less)		
Hearing loss *** (dB)	0 decibels	3.70 decibels	⊕◯◯◯[1,2,3] Very low
	MD: 3.7 decibels more (Margin of error: 8.29 less than 15.69 more)		
Frequency of vertigo attacks per year	One review [4] that was based on one trial (28 patients) [73] reported that gentamicin therapy produced no change in tinnitus.		⊕◯◯◯[1,2] Very low
Tinnitus	One review [4] that was based on one trial (28 patients) [73] reported that gentamicin therapy produced no change in tinnitus.		⊕⊕◯◯[1,2] Low
Quality of life	Two reviews [4], [12] reported that none of the trials assessed quality of life.		-
Adverse effects	One review [4] reported that none of the included trials assessed other adverse effects.		-

Margin of error: 95% confidence interval (CI).
MD: Mean difference.
GRADE: Evidence grades of the GRADE Working Group (see later).

* The average **WITHOUT intratympanic gentamicin** is based on the average of the study of greater weight of the control group of the studies. The average **WITH intratympanic gentamicin** (and its margin of error) is calculated from the difference in means (and its margin of error).
** The intensity of vertigo was evaluated with an unspecified scale ranging from zero to three points that is interpreted as: severe (three points), moderate (two points), mild (one point) and none (zero points) [73].
*** Measured in decibels (dB), where higher decibels are considered to be greater hearing loss.

[1] The certainty of the evidence was downgraded in one level for risk of bias, as the trial [73] did not provide information on the generation of the randomization sequence and the follow-up was less than 2 years. In the case of the outcome "Frequency of vertigo attacks per year", two levels of certainty of evidence were downgraded due to risk of bias, since the trial [73] presented limitations associated with the generation of randomization sequence, attrition (no clear information on the loss of patients in the placebo group) and selective reporting.
[2] The certainty of the evidence was downgraded in one level due to imprecision as different decisions would be made at each end of the confidence interval. In the case of the outcomes of attacks of vertigo and tinnitus, a level of certainty of the evidence was downgraded for this reason, due to the small sample size of the trial and the infrequency of the event.
[3] The certainty of the evidence was downgraded in one level for inconsistency, as the different studies show contradictory results.

Follow the link to access the interactive version of this table *(Interactive Summary of Findings – iSoF)*

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

This evidence applies to adults with diagnosis of refractory progressive Ménière's disease, resistant to treatment or to patients with severely impaired hearing.

It does not apply to patients with Ménière's disease who have received previous surgical treatment or with a good response to therapy.

About the outcomes included in this summary

The outcomes presented in the summary of findings table are those considered critical for decision making by the authors of this summary, and in general agree with the systematic reviews identified.

Although adverse effects and quality of life outcomes were assessed by systematic reviews, none of the identified trials reported information.

Balance between benefits and risks, and certainty of the evidence

The current evidence suggests that intratympanic gentamicin may reduce the symptoms associated with refractory Ménière's disease reflected in the intensity of vertigo, and that there would also be no differences in the management of tinnitus, but the certainty of the evidence is low.

On the other hand, its effect on the frequency of vertigo attacks and hearing loss is uncertain, since the certainty of the evidence was evaluated as very low.

Given these conditions and the lack of evidence related to quality of life or other adverse effects associated with therapy that could add relevant information, it is necessary to have an adequate estimate of the effect to perform a correct analysis between risks and benefits.

Resource considerations

Intratympanic gentamicin is a low-cost intervention compared to other more aggressive alternative treatments such as labyrinthectomy or vestibular neurectomy, which would imply additional costs associated with the surgical procedure.

However, it is not possible to provide an adequate cost-benefit analysis because there is uncertainty about the effect of gentamicin in the control of Ménière's disease.

What would patients and their doctors think about this intervention

Based on the evidence provided in this summary, most patients and clinicians should not lean in favor of its use, since it does not allow to assert whether there is an effect on the control of vertigo, tinnitus management and quality of life.

However, given the lack of better therapeutic alternatives for the management of intractable Ménière's disease, it is expected that some clinicians or patients would use an alternative whose benefit is not proven.

Differences between this summary and other sources

The conclusions of this summary are concordant with those reached in five systematic reviews, that identify an important limitation of the existing evidence.

On the other hand, 12 of the 13 systematic reviews identified [3], [4], [5], [6], [7], [8], [10], [11], [12], [13] , [14], [15] conclude that intratympanic gentamicin would be an effective treatment for vertigo management, especially using the weekly titration protocol [15] and that low doses would be safer when long regimens are used [7].

Both the 'Guidelines of the French Otorhinolaryngology-Head and Neck Surgery Society on Ménière's disease' [97], and the European Academy of Otology and Neurotology Vertigo Guidelines [98] conclude intratympanic gentamicin is effective for the control of vertigo, reporting low risk of hearing impairment when small doses are used.

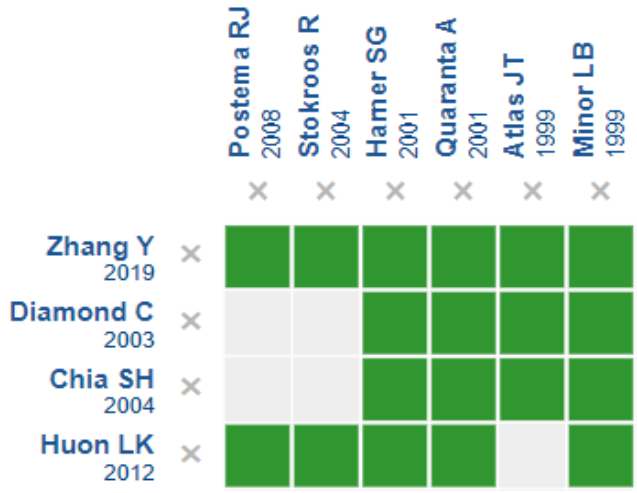
Could this evidence change in the future?

It is very likely that future research will modify the conclusion of this summary, due to the existing uncertainty, especially with regard to hearing loss and frequency of vertigo attacks, since the certainty of the evidence is very low.

A search in the PROSPERO database and in the platform of clinical trials of the World Health Organization, identified there were three ongoing systematic [99], [100], [101] but no trials associated with the question of interest.

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:** Gentamicin versus placebo or not treatment in Meniere´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.

Referencias

1. Moskowitz, H. and Dinces, E. (2019). Meniere disease. [online] Uptodate. Available at: https://www.uptodate.com/contents/meniere-disease?search=intractable%20meniere%20definition&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2 [Accessed 6 May 2019].
2. Ren H, Yin T, Lu Y, Kong W, Ren J. Intratympanic dexamethasone injections for refractory Meniere' s disease. Int J Clin Exp Med. 2015 Apr 15;8(4):6016-23. eCollection 2015. PubMed PMID: 26131198; PubMed Central PMCID: PMC4483845.
3. Ballard DP, Sukato DC, Timashpolsky A, Babu SC, Rosenfeld RM, Hanson M. Quality-of-Life Outcomes following Surgical Treatment of Ménière's Disease: A Systematic Review and Meta-analysis. Otolaryngol Head Neck Surg. 2019 Feb;160(2):232-238. doi: 10.1177/0194599818803612. Epub 2018 Oct 9. PubMed PMID: 30300093.
4. Pullens B, van Benthem PP. Intratympanic gentamicin for Ménière's disease or syndrome. Cochrane Database Syst Rev. 2011 Mar 16;(3):CD008234. doi: 10.1002/14651858.CD008234.pub2. Review. PubMed PMID: 21412917.
5. Cao Z, Yue F, Huang W, Rajenderkumar D, Zhao F. Different medications for the treatment of Ménière's disease by intratympanic injection: a systematic review and network meta-analysis. Clin Otolaryngol. 2019 Apr 26. doi: 10.1111/coa.13350. [Epub ahead of print] PubMed PMID: 31025490.
6. Chia SH, Gamst AC, Anderson JP, Harris JP. Intratympanic gentamicin therapy for Ménière's disease: a meta-analysis. Otol Neurotol. 2004 Jul;25(4):544-52. PubMed PMID: 15241234.
7. Cohen-Kerem R, Kisilevsky V, Einarson TR, Kozer E, Koren G, Rutka JA. Intratympanic gentamicin for Menière's disease: a meta-analysis. Laryngoscope. 2004 Dec;114(12):2085-91. Review. PubMed PMID: 15564826.

8. Diamond C, O'Connell DA, Hornig JD, Liu R. Systematic review of intratympanic gentamicin in Meniere's disease. J Otolaryngol. 2003 Dec;32(6):351-61. Review. PubMed PMID: 14967079.
9. Hao, Weiming and Yu, Huiqian and Li, Huawei, Effects of Intratympanic Gentamicin and Intratympanic Glucocorticoids in Ménière's Disease: A Network Meta-Analysis of Randomized, Controlled Trials (April 12, 2019). Available at SSRN: https://ssrn.com/abstract=3371077
10. Huon LK, Fang TY, Wang PC. Outcomes of intratympanic gentamicin injection to treat Ménière's disease. Otol Neurotol. 2012 Jul;33(5):706-14. doi: 10.1097/MAO.0b013e318259b3b1. Review. PubMed PMID: 22699980.
11. Marques PS, Dias CC, Perez-Fernandez N, Spratley J. Instrumental head impulse test changes after intratympanic gentamicin for unilateral definite Ménière's disease: A systematic review and meta-analysis. Auris Nasus Larynx. 2018 Oct;45(5):943-951. doi: 10.1016/j.anl.2018.01.001. Epub 2018 May 7. Review. PubMed PMID: 29402608.
12. Syed MI, Ilan O, Nassar J, Rutka JA. Intratympanic therapy in Meniere's syndrome or disease: up to date evidence for clinical practice. Clin Otolaryngol. 2015 Dec;40(6):682-90. doi: 10.1111/coa.12449. Review. PubMed PMID: 25916787.
13. Tuvang, E. (2016). Syed, M., Ilan, O., Nassar, J. and Rutka, J. (2015). Intratympanic therapy in Meniere's syndrome or disease: up to date evidence for clinical practice. Clinical Otolaryngology, 40(6), pp.682-690. Umeå University, Sweden. [online] Available at: http://www.diva-portal.org/smash/get/diva2:923242/FULLTEXT01.pdf [Accessed 2 May 2019].
14. Vlastarakos PV, Iacovou E, Nikolopoulos TP. Is gentamycin delivery via sustained-release vehicles a safe and effective treatment for refractory Meniere's disease? A critical analysis of published interventional studies. Eur Arch Otorhinolaryngol. 2017 Mar;274(3):1309-1315. doi: 10.1007/s00405-016-4294-9. Epub 2016 Sep 13. Review. PubMed PMID: 27623821.
15. Zhang Y, Fu J, Lin H, Shen C, Wang X, Wu J. The Clinical Outcomes After Intratympanic Gentamicin Injection to Treat Menière's Disease: A Meta-analysis. Otol Neurotol. 2019 Apr;40(4):419-429. doi: 10.1097/MAO.0000000000002159. PubMed PMID: 30870347.
16. Atlas JT, Parnes LS. Intratympanic gentamicin titration therapy for intractable Meniere's disease. Am J Otol. 1999 May;20(3):357-63. PubMed PMID:10337978.
17. Beck C. Intratympanic application of gentamicin for treatment of Menière's disease. Keio J Med. 1986 Mar;35(1):36-41. PubMed PMID: 3747323.
18. Beck C, Schmidt CL. 10 years of experience with intratympanally applied streptomycin (gentamycin) in the therapy of Morbus Menière. Arch Otorhinolaryngol. 1978 Sep 28;221(2):149-52. PubMed PMID: 751619.
19. Bertino G, Durso D, Manfrin M, Casati L, Mira E. Intratympanic gentamicin in monolateral Meniere's disease: our experience. Eur Arch Otorhinolaryngol. 2006 Mar;263(3):271-5. Epub 2005 Jul 15. PubMed PMID: 16021460.
20. Bodmer D, Morong S, Stewart C, Alexander A, Chen JM, Nedzelski JM. Long-term vertigo control in patients after intratympanic gentamicin instillation for Ménière's disease. Otol Neurotol. 2007 Dec;28(8):1140-4. PubMed PMID: 18084826.
21. Boleas-Aguirre MS, Sánchez-Ferrandiz N, Guillén-Grima F, Perez N. Long-term disability of class A patients with Ménière's disease after treatment with intratympanic gentamicin. Laryngoscope. 2007 Aug;117(8):1474-81. PubMed PMID: 17607149.
22. Bottrill I, Wills AD, Mitchell AL. Intratympanic gentamicin for unilateral Meniere's disease: results of therapy. Clin Otolaryngol Allied Sci. 2003 Apr;28(2):133-41. PubMed PMID: 12680832.
23. Bremer HG, van Rooy I, Pullens B, Colijn C, Stegeman I, van der Zaag-Loonen HJ, van Benthem PP, Klis SF, Grolman W, Bruintjes TD. Intratympanic gentamicin treatment for Ménière's disease: a randomized, double-blind, placebo-controlled trial on dose efficacy - results of a prematurely ended study. Trials. 2014 Aug 18;15:328. doi: 10.1186/1745-6215-15-328. PubMed PMID: 25135244; PubMed Central PMCID: PMC4141100.
24. Carey JP, Minor LB, Peng GC, Della Santina CC, Cremer PD, Haslwanter T. Changes in the three-dimensional angular vestibulo-ocular reflex following intratympanic gentamicin for Ménière's disease. J Assoc Res Otolaryngol. 2002 Dec;3(4):430-43. Epub 2002 Mar 26. PubMed PMID: 12486598; PubMed Central PMCID: PMC3202443.
25. Casani A, Nuti D, Franceschini SS, Gaudini E, Dallan I. Transtympanic gentamicin and fibrin tissue adhesive for treatment of unilateral Menière's disease: effects on vestibular function. Otolaryngol Head Neck Surg. 2005 Dec;133(6):929-35. PubMed PMID: 16360516.
26. Corsten, M., Marsan, J., Schramm, D. and Robichaud, J. (1997). Treatment of intractable Menière's disease with intratympanic gentamicin: review of the University of Ottawa experience. J Otolaryngol., [online] 26(6), pp.361-4. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9438932 [Accessed 2 May 2019].
27. Crane BT, Minor LB, Della Santina CC, Carey JP. Middle ear exploration in patients with Ménière's disease who have failed outpatient intratympanic gentamicin therapy. Otol Neurotol. 2009 Aug;30(5):619-24. doi: 10.1097/MAO.0b013e3181a66d2b. PubMed PMID: 19503016.
28. Daneshi A, Jahandideh H, Pousti SB, Mohammadi S. One-shot, low-dosage intratympanic gentamicin for Ménière's disease: Clinical, posturographic and vestibular test findings. Iran J Neurol. 2014;13(1):33-9. PubMed PMID: 24800045; PubMed Central PMCID: PMC3968355.
29. De Beer L, Stokroos R, Kingma H. Intratympanic gentamicin therapy for intractable Ménière's disease. Acta Otolaryngol. 2007 Jun;127(6):605-12. PubMed PMID: 17503229.
30. De Valck CF, Van Rompaey V, Wuyts EL, Van de Heyning PH. Tenotomy of the tensor tympani and stapedius tendons in Ménière's disease. B-ENT. 2009;5(1):1-6. PubMed PMID: 19455992.
31. DeCicco, M., Hoffer, M. and RD, K. (1998). Round-window microcatheter administered microdose gentamicin: results from treatment of tinnitus associated with Ménière's disease. Int Tin- nitus J. [online] Available at: https://www.epistemonikos.org/es/documents/5b262d51938b7380a0b1d4656e9105c9843f9a69 [Accessed 6 May 2019].
32. Delgado LP, Rodrigo JF, Peña PA. Intratympanic gentamicin in Ménière's disease: our experience. J Laryngol Otol. 2011 Apr;125(4):363-9. doi: 10.1017/S0022215111000053. Epub 2011 Feb 15. PubMed PMID: 21320380.
33. Driscoll CL, Kasperbauer JL, Facer GW, Harner SG, Beatty CW. Low-dose intratympanic gentamicin and the treatment of Meniere's disease: preliminary results. Laryngoscope. 1997 Jan;107(1):83-9. PubMed PMID: 9001270.
34. Eklund S, Pyykkö I, Aalto H, Ishizaki H, Vasama JP. Effect of intratympanic gentamicin on hearing and tinnitus in Meniere's disease. Am J Otol. 1999 May;20(3):350-6. PubMed PMID: 10337977.
35. Gabra N, Saliba I. The effect of intratympanic methylprednisolone and gentamicin injection on Ménière's disease. Otolaryngol Head Neck Surg. 2013 Apr;148(4):642-7. doi: 10.1177/0194599812472882. Epub 2013 Jan 11. PubMed PMID: 23314159.
36. Gayathri, H. and Rao, S. (2010). Low dose intratympanic gentamicin for controlof intractable vertigo. Indian J Otol. [online] Available at:

https://www.epistemonikos.org/es/documents/64c4806384d719d50767b00f6174046b73bc3bb1 [Accessed 6 May 2019].
37. Harner SG, Driscoll CL, Facer GW, Beatty CW, McDonald TJ. Long-term follow-up of transtympanic gentamicin for Ménière's syndrome. Otol Neurotol. 2001 Mar;22(2):210-4. PubMed PMID: 11300271.
38. Helling K, Schönfeld U, Clarke AH. Treatment of Ménière's disease by low-dosage intratympanic gentamicin application: effect on otolith function. Laryngoscope. 2007 Dec;117(12):2244-50. PubMed PMID: 17909448.
39. Hill SL 3rd, Digges EN, Silverstein H. Long-term follow-up after gentamicin application via the Silverstein MicroWick in the treatment of Ménière's disease. Ear Nose Throat J. 2006 Aug;85(8):494, 496, 498. PubMed PMID: 16999055.
40. Hirsch BE, Kamerer DB. Intratympanic gentamicin therapy for Ménière's disease. Am J Otol. 1997 Jan;18(1):44-51. PubMed PMID: 8989951.
41. Hoffer ME, Kopke RD, Weisskopf P, Gottshall K, Allen K, Wester D. Microdose gentamicin administration via the round window microcatheter: results in patients with Meniere's disease. Ann N Y Acad Sci. 2001 Oct;942:46-51. PubMed PMID: 11710484.
42. Horii A, Saika T, Uno A, Nishiike S, Mitani K, Nishimura M, Kitahara T, Fukushima M, Nakagawa A, Masumura C, Sasaki T, Kizawa K, Kubo T. Factors relating to the vertigo control and hearing changes following intratympanic gentamicin for intractable Ménière's disease. Otol Neurotol. 2006 Sep;27(6):896-900. PubMed PMID: 16788414.
43. Hsieh LC, Lin HC, Tsai HT, Ko YC, Shu MT, Lin LH. High-dose intratympanic gentamicin instillations for treatment of Meniere's disease: long-term results. Acta Otolaryngol. 2009 Dec;129(12):1420-4. doi: 10.3109/00016480902856612. PubMed PMID: 19922092.
44. Inoue H, Uchi Y, Nogami K, Uemura T. Low-dose intratympanic gentamicin treatment of Menière's disease. Eur Arch Otorhinolaryngol. 1994;251 Suppl 1:S12-4. PubMed PMID: 11894767.
45. Junet P, Karkas A, Dumas G, Quesada JL, Schmerber S. Vestibular results after intratympanic gentamicin therapy in disabling Menière's disease. Eur Arch Otorhinolaryngol. 2016 Oct;273(10):3011-8. doi: 10.1007/s00405-015-3889-x. Epub 2016 Jan 16. PubMed PMID: 26780342.
46. Jung J, Chun J, Kim N, Kim Y, Lee WS. Evaluation of quality of life after intratympanic streptomycin injection in patients with Ménière's disease. Otol Neurotol. 2008 Sep;29(6):816-23. doi: 10.1097/MAO.0b013e31817ef4e3. PubMed PMID: 18617871.
47. Kaasinen S, Pyykkö I, Ishizaki H, Aalto H. Intratympanic gentamicin in Meniere's disease. Acta Otolaryngol. 1998 Jun;118(3):294-8. PubMed PMID: 9655201
48. Kaplan DM, Nedzelski JM, Chen JM, Shipp DB. Intratympanic gentamicin for the treatment of unilateral Meniere's disease. Laryngoscope. 2000 Aug;110(8):1298-305. PubMed PMID: 10942130
49. Kaplan DM, Nedzelski JM, Al-Abidi A, Chen JM, Shipp DB. Hearing loss following intratympanic instillation of gentamicin for the treatment of unilateral Meniere's disease. J Otolaryngol. 2002 Apr;31(2):106-11. PubMed PMID: 12019738.
50. Katzenell U, Gordon M, Page M. Intratympanic gentamicin injections for the treatment of Ménière's disease. Otolaryngol Head Neck Surg. 2010 Nov;143(5 Suppl 3):S24-9. doi: 10.1016/j.otohns.2010.05.028. PubMed PMID: 20970688.
51. Kyrodimos E, Aidonis I, Sismanis A. Hearing results following intratympanic gentamicin perfusion for Ménière's disease. J Laryngol Otol. 2009 Apr;123(4):379-82. doi: 10.1017/S0022215108003150. Epub 2008 Oct 28. PubMed PMID: 18954493.
52. Laitakari K. Intratympanic gentamycin in severe Ménière's disease. Clin Otolaryngol Allied Sci. 1990 Dec;15(6):545-8. PubMed PMID: 2073763.
53. Lange G, Maurer J, Mann W. Long-term results after interval therapy with intratympanic gentamicin for Menière's disease. Laryngoscope. 2004 Jan;114(1):102-5. PubMed PMID: 14710003.
54. Lange G. Transtympanic gentamycin in the treatment of Ménière's disease. Rev Laryngol Otol Rhinol (Bord). 1995;116(2):151-2. PubMed PMID: 7569379.
55. Leone CA, Mosca F, Mincione A. [Ablation therapy with gentamycin in the treatment of Meniere's disease]. Acta Otorhinolaryngol Ital. 2000 Oct;20(5):322-9. Italian. PubMed PMID: 11284259.
56. Lin FR, Migliaccio AA, Haslwanter T, Minor LB, Carey JP. Angular vestibulo-ocular reflex gains correlate with vertigo control after intratympanic gentamicin treatment for Meniere's disease. Ann Otol Rhinol Laryngol. 2005 Oct;114(10):777-85. PubMed PMID: 16285268; PubMed Central PMCID: PMC4477784.
57. Liu H, Zhang T, Wu Q, Zhang Y, Dai C. End-point indicators of low-dose intra-tympanic gentamicin in management of Ménière's disease. Acta Otolaryngol. 2017 Feb;137(2):136-143. doi: 10.1080/00016489.2016.1224921. Epub 2016 Sep 9. PubMed PMID: 27608722.
58. Longridge NS, Mallinson AI. Low-dose intratympanic gentamicin treatment for dizziness in Ménière's disease. J Otolaryngol. 2000 Feb;29(1):35-9. PubMed PMID: 10709170.
59. MacKeith SA, Whiteside OJ, Mawby T, Bottrill ID. Middle ear gentamicin-soaked pledgets in the treatment of Ménière's disease. Otol Neurotol. 2014 Feb;35(2):305-9. doi: 10.1097/MAO.0b013e3182a5d304. PubMed PMID: 24448291.
60. Magnusson M, Padoan S. Delayed onset of ototoxic effects of gentamicin in treatment of Menière's disease. Rationale for extremely low dose therapy. Acta Otolaryngol. 1991;111(4):671-6. PubMed PMID: 1950529.
61. Marques P, Manrique-Huarte R, Perez-Fernandez N. Single intratympanic gentamicin injection in Ménière's disease: VOR change and prognostic usefulness. Laryngoscope. 2015 Aug;125(8):1915-20. doi: 10.1002/lary.25156. Epub 2015 Jan 30. PubMed PMID: 25641686.
62. Martin E, Perez N. Hearing loss after intratympanic gentamicin therapy for unilateral Ménière's Disease. Otol Neurotol. 2003 Sep;24(5):800-6. PubMed PMID: 14501459.
63. Marzo SJ, Leonetti JP. Intratympanic gentamicin therapy for persistent vertigo after endolymphatic sac surgery. Otolaryngol Head Neck Surg. 2002 Jan;126(1):31-3. PubMed PMID: 11821762.
64. McFeely WJ, Singleton GT, Rodriguez FJ, Antonelli PJ. Intratympanic gentamicin treatment for Meniere's disease. Otolaryngol Head Neck Surg. 1998 May;118(5):589-96. PubMed PMID: 9591855.
65. Minor LB. Intratympanic gentamicin for control of vertigo in Meniere's disease: vestibular signs that specify completion of therapy. Am J Otol. 1999 Mar;20(2):209-19. PubMed PMID: 10100525.
66. Murofushi T, Halmagyi GM, Yavor RA. Intratympanic gentamicin in Ménière's disease: results of therapy. Am J Otol. 1997 Jan;18(1):52-7. PubMed PMID: 8989952.
67. Nedzelski JM, Chiong CM, Fradet G, Schessel DA, Bryce GE, Pfleiderer AG. Intratympanic gentamicin instillation as treatment of unilateral Menière's disease: update of an ongoing study. Am J Otol. 1993 May;14(3):278-82. Review. PubMed PMID: 8372926.
68. Odkvist, L. (1988). Middle ear ototoxic treatment for inner ear disease. Acta Otolaryngol. [online] Available at: https://www.epistemonikos.org/es/documents/bf95dcdf70a8c981b12c9d9bd892a5820955040c [Accessed 6 May 2019].
69. Paradis J, Hu A, Parnes LS. Endolymphatic sac surgery versus intratympanic gentamicin for the treatment of intractable Ménière's

disease: a retrospective review with survey. Otol Neurotol. 2013 Oct;34(8):1434-7. doi: 10.1097/MAO.0b013e3182908b28. PubMed PMID: 23846192.

70. Perez N, Martín E, García-Tapia R. Intratympanic gentamicin for intractable Meniere's disease. Laryngoscope. 2003 Mar;113(3):456-64. PubMed PMID: 12616197.
71. Perez N, Martin E, Zubieta JL, Romero MD, Garcia-Tapia R. Benign paroxysmal positional vertigo in patients with Ménière's disease treated with intratympanic gentamycin. Laryngoscope. 2002 Jun;112(6):1104-9. PubMed PMID: 12160282.
72. Pfleiderer AG. The current role of local intratympanic gentamicin therapy in the management of unilateral Menière's disease. Clin Otolaryngol Allied Sci. 1998 Feb;23(1):34-41. PubMed PMID: 9563663.
73. Postema RJ, Kingma CM, Wit HP, Albers FW, Van Der Laan BF. Intratympanic gentamicin therapy for control of vertigo in unilateral Menire's disease: a prospective, double-blind, randomized, placebo-controlled trial. Acta Otolaryngol. 2008 Aug;128(8):876-80. doi: 10.1080/00016480701762458. PubMed PMID: 18607963.
74. Quaglieri S, Gatti O, Rebecchi E, Manfrin M, Tinelli C, Mira E, Benazzo M. Intratympanic gentamicin treatment 'as needed' for Meniere's disease. Long-term analysis using the Kaplan-Meier method. Eur Arch Otorhinolaryngol. 2014 Jun;271(6):1443-9. doi: 10.1007/s00405-013-2597-7. Epub 2013 Jun 19. PubMed PMID: 23778723.
75. Quaranta A, Aloisi A, De Benedittis G, Scaringi A. Intratympanic therapy for Ménière's disease. High-concentration gentamicin with round-window protection. Ann N Y Acad Sci. 1999 Nov 28;884:410-24. PubMed PMID: 10842610.
76. Quaranta A, Scaringi A, Aloidi A, Quaranta N, Salonna I. Intratympanic therapy for Ménière's disease: effect of administration of low concentration of gentamicin. Acta Otolaryngol. 2001 Apr;121(3):387-92. PubMed PMID: 11425206.
77. Quaranta, A., Aloisi, A., De Benedittis, D. and Scaringi, A. (1999). Intratympanic therapy for Meniere's disease. Ann N Y Acad Sci. [online] Available at: https://www.epistemonikos.org/es/documents/972e5fb4e07181ccc14fa6e9a21a4d57723c0149 [Accessed 6 May 2019].
78. Rah YC, Han JJ, Park J, Choi BY, Koo JW. Management of intractable Ménière's disease after intratympanic injection of gentamicin. Laryngoscope. 2015 Apr;125(4):972-8. doi: 10.1002/lary.25009. Epub 2014 Nov 1. PubMed PMID: 25363447.
79. Rauch SD, Oas JG. Intratympanic gentamicin for treatment of intractable Meniere's disease: a preliminary report. Laryngoscope. 1997 Jan;107(1):49-55. PubMed PMID: 9001265.
80. Sala T. Transtympanic administration of aminoglycosides in patients with Menière's disease. Arch Otorhinolaryngol. 1988;245(5):293-6. PubMed PMID: 3245801.
81. Sala T. Transtympanic gentamicin in the treatment of Meniére's disease. Auris Nasus Larynx. 1997 Jul;24(3):239-46. PubMed PMID: 9251852.
82. Schoendorf J, Neugebauer P, Michel O. Continuous intratympanic infusion of gentamicin via a microcatheter in Menière's disease. Otolaryngol Head Neck Surg. 2001 Feb;124(2):203-7. PubMed PMID: 11226958.
83. Seidman M. Continuous gentamicin therapy using an IntraEAR microcatheter for Meniere's disease: a retrospective study. Otolaryngol Head Neck Surg. 2002 Mar;126(3):244-56. PubMed PMID: 11956532.
84. Shamas IU. Short Term Results of Intra Tympanic Gentamicin and Dexamethasone on Hearing and Tinnitus in Meniere's disease: A Case Control Study. Int Tinnitus J. 2017 Jun 1;21(1):21-23. doi: 10.5935/0946-5448.20170005. PubMed PMID: 28723597.
85. Shea PF, Richey PA, Wan JY, Stevens SR. Hearing results and quality of life after streptomycin/dexamethasone perfusion for Meniere's disease. Laryngoscope. 2012 Jan;122(1):204-11. doi: 10.1002/lary.22362. PubMed PMID: 22183636.
86. Silverstein H, Wazen J, Van Ess MJ, Daugherty J, Alameda YA. Intratympanic gentamicin treatment of patients with Ménière's disease with normal hearing. Otolaryngol Head Neck Surg. 2010 Apr;142(4):570-5. doi: 10.1016/j.otohns.2009.12.009. PubMed PMID: 20304280.
87. Stokroos R, Kingma H. Selective vestibular ablation by intratympanic gentamicin in patients with unilateral active Ménière's disease: a prospective, double-blind, placebo-controlled, randomized clinical trial. Acta Otolaryngol. 2004 Mar;124(2):172-5. PubMed PMID: 15072419.
88. Suryanarayanan R, Cook JA. Long-term results of gentamicin inner ear perfusion in Ménière's disease. J Laryngol Otol. 2004 Jul;118(7):489-95. PubMed PMID: 15318953.
89. Suryanarayanan R, Srinivasan VR, O'Sullivan G. Transtympanic gentamicin treatment using Silverstein MicroWick in Ménière's disease patients: long term outcome. J Laryngol Otol. 2009 Jan;123(1):45-9. doi: 10.1017/S0022215108002776. Epub 2008 Jun 4. PubMed PMID: 18533050.
90. Thomsen J, Charabi S, Tos M. Preliminary results of a new delivery system for gentamicin to the inner ear in patients with Meniere's disease. Eur Arch Otorhinolaryngol. 2000;257(7):362-5. PubMed PMID: 11052245.
91. Watanabe S, Kato I, Takahashi K, Yoshino K, Takeyama I. Indications and results of gentamycin injection into the middle ear of patients with meniére's disease. Acta Otolaryngol Suppl. 1995;519:282-5. PubMed PMID: 7610887.
92. Wu IC, Minor LB. Long-term hearing outcome in patients receiving intratympanic gentamicin for Ménière's disease. Laryngoscope. 2003 May;113(5):815-20. PubMed PMID: 12792316.
93. Yamazaki T, Hayashi M, Komatsuzaki A. Intratympanic gentamicin therapy for Menière's disease placed by a tubal catheter with systematic isosorbide. Acta Otolaryngol Suppl. 1991;481:613-6. PubMed PMID: 1927484.
94. Yetiser S, Kertmen M. Intratympanic gentamicin in Menière's disease: the impact on tinnitus. Int J Audiol. 2002 Sep;41(6):363-70. PubMed PMID: 12353609.
95. Youssef TF, Poe DS. Intratympanic gentamicin injection for the treatment of Meniere's disease. Am J Otol. 1998 Jul;19(4):435-42. PubMed PMID: 9661751.
96. Marín Garrido C, Fraile Rodrigo J, Naya Gálvez MJ, Samperiz LC, Hernández Montero E, Ortiz García A. [Intra-tympanic gentamicin in the treatment of Ménière's disease: preliminary results]. Acta Otorrinolaringol Esp. 2002 May;53(5):326-32. Spanish. PubMed PMID: 12185867.
97. Nevoux J, Franco-Vidal V, Bouccara D, Parietti-Winkler C, Uziel A, Chays A, Dubernard X, Couloigner V, Darrouzet V, Mom T; Groupe de Travail de la SFORL. Diagnostic and therapeutic strategy in Menière's disease. Guidelines of the French Otorhinolaryngology-Head and Neck Surgery Society (SFORL). Eur Ann Otorhinolaryngol Head Neck Dis. 2017 Jan 3. pii: S1879-7296(16)30222-8.
98. Magnan, J., Özgirgin, O., Trabalzini, F., Lacour, M., Lopez, A., Magnusson, M., Alpin, E., Philippe, J., Nuti, D. and Mandala, M. (2018). European Position Statement on Diagnosis, and Treatment of Meniere's Disease*. J Int Adv Otol, [online] 14(2), pp.317-321. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6354459/ [Accessed 6 May 2019].
99. Weiming Hao, Huiqian Yu, Huawei Li. The effects of intratympanic therapy of Ménière's disease: a network meta-analysis. PROSPERO

2018 CRD42018114389 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018114389

100. Louise Devantier, Jesper Hvass Schmidt, Frank Liviu-Adelin Guldfred, Dan Dupont Hougaard, Bjarki Djurhuus, Mina Nicole Händel, Henriette Callesen. A systematic review and meta-analysis of treatment of patients with Menieres disease with gentamicin. PROSPERO 2018 CRD42018110119 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018110119

101. Kinga Harmat, Adrienne Németh. Efficacy and safety of intratympanic steroid and gentamicin treatment of Ménière's disease: a meta-analysis. PROSPERO 2018 CRD42018095413 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018095413

Correspondence to
Centro Evidencia UC
Pontificia Universidad Católica de Chile
Diagonal Paraguay 476
Santiago
Chile