

**Current state of evidence for endolymphatic sac surgery in Menière's disease
a systematic review**

Devantier, Louise; Schmidt, Jesper Hvass; Djurhuus, Bjarki Ditlev; Hougaard, Dan Dupont; Händel, Mina Nicole; Liviu-Adelin Guldfred, Frank; Edemann-Callesen, Henriette

Published in:
Acta Oto-Laryngologica

DOI:
10.1080/00016489.2019.1657240

Publication date:
2019

Document version:
Accepted manuscript

Citation for published version (APA):
Devantier, L., Schmidt, J. H., Djurhuus, B. D., Hougaard, D. D., Händel, M. N., Liviu-Adelin Guldred, F., & Edemann-Callesen, H. (2019). Current state of evidence for endolymphatic sac surgery in Menière's disease: a systematic review. *Acta Oto-Laryngologica*, 139(11), 953-958. <https://doi.org/10.1080/00016489.2019.1657240>

Go to publication entry in University of Southern Denmark's Research Portal

Terms of use

This work is brought to you by the University of Southern Denmark.
Unless otherwise specified it has been shared according to the terms for self-archiving.
If no other license is stated, these terms apply:

- You may download this work for personal use only.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying this open access version

If you believe that this document breaches copyright please contact us providing details and we will investigate your claim.
Please direct all enquiries to puresupport@bib.sdu.dk

Current state of evidence for endolymphatic sac surgery in Menière's disease: a systematic review

Authors and affiliations:

MD Louise Devantier^{1,2}, MD PhD Jesper Hvass Schmidt^{3, 4}, MD PhD Bjarki Ditlev Djurhuus⁵, MD Dan Dupont Hougaard⁶, MD PhD Mina Nicole Händel^{7, 8}, MD Frank Liviu-Adelin Guldred⁹, Msc Henriette Edemann-Callesen⁷.

- 1) Department of Clinical Medicine, Aarhus University, Aarhus, Denmark.
- 2) Department of Oto-Rhino-Laryngology, Regional Hospital West Jutland, Holstebro, Denmark
- 3) Department of ORL, Head and Neck Surgery and Audiology, Odense University Hospital, Odense C, Denmark.
- 4) Department of Clinical Research, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark
- 5) Department of Ear, Nose, Throat and Maxillofacial Surgery, Zealand University Hospital, Koege, Denmark
- 6) Department of Otolaryngology, Head & Neck Surgery and Audiology, Aalborg University Hospital, Aalborg, Denmark.
- 7) The Danish Health Authority, Copenhagen, Denmark
- 8) The Parker Institute, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Copenhagen, Denmark
- 9) Ear, Nose and Throat Clinic, Faxe, Denmark.

Correspondence: Louise Devantier, MD. Department of Clinical Medicine, Aarhus University,

Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark (louisedevantier@clin.au.dk)

Abstract

Background: Endolymphatic sac surgery is an invasive procedure recommended to patients with Menière's disease.

Aims/Objectives: To provide an overview and quality assessment of the existing evidence and to provide an updated assessment of the utility of endolymphatic sac surgery in Menière's disease.

Material and Methods: We performed a systematic literature search for systematic reviews and randomized controlled trials (RCTs). The AMSTAR tool was used to assess the quality of systematic reviews and the Cochrane risk of bias tool for RCTs. The overall certainty of effects for the individual outcomes was evaluated using the GRADE approach.

Results: One systematic review of high quality matched the inclusion criteria, and included three RCTs. An updated literature search from the last search date of the included review provided no further relevant RCTs. The identified RCTs individually reported a positive effect of both the placebo and active treatment groups following surgery, strongly indicative of a placebo effect. The overall certainty of the effect very low.

Conclusions and Significance: There is still a lack of high quality research suggesting that endolymphatic sac surgery provides a significant amount of symptomatic relief for Menière's patients.

1 **Introduction**

2 Menière's disease is characterized by spontaneous episodes of vertigo combined with tinnitus, aural
3 fullness and fluctuating low frequency sensorineural hearing loss. It is a chronic inner ear disease
4 where both hearing loss and vestibular deficits generally progress regardless of treatment. Even
5 though the disease was first described more than 150 years ago, the etiology remains uncertain [1].
6 Endolymphatic hydrops due to endolymphatic malabsorption in the labyrinth's endolymphatic sac
7 is considered a hallmark of Menière's disease [1]. Within recent years it has become possible to
8 visualize endolymphatic hydrops with gadolinium magnetic resonance imaging (MRI). However,
9 this has not been globally implemented and it is not a requirement in the newest set of diagnostic
10 criteria from the Barany society [2]. As of now, there is no cure for Menière's disease. Wide ranges
11 of different treatment modalities exist including dietary salt restriction as well as treatment with
12 diuretics in an attempt to influence the endolymphatic pressure imbalance. Severely disabled
13 patients with Menière disease, who have failed to respond to other available treatment modalities,
14 may be offered endolymphatic sac surgery. Endolymphatic sac surgery is performed using different
15 surgical procedures such as endolymphatic sac decompression and duct blockage. Both methods
16 tend to regulate the endolymphatic flow using different approaches.

17 Endolymphatic sac surgery is an invasive procedure and therefore high-quality evidence is essential
18 to evaluate its potential positive effects and associated risks, especially in relation to hearing loss.
19 The objective of this review was to provide an overview and quality assessment of the existing
20 evidence and, based on the identified literature, to provide an update on the usage of endolymphatic
21 sac surgery in Menière's disease. The primary focus of this particular systematic review was
22 patients (≥ 18 years of age) diagnosed with either definite or probable Menière's disease undergoing
23 endolymphatic sac surgery compared to no surgery/placebo surgery. Specifically, we sought to
24 evaluate the effects of this treatment in regards to frequency, duration and severity of vertiginous

25 attacks, serious adverse events as well as quality of life, impact on daily life, tinnitus, patient
26 reported operative effect, and hearing loss.

27

28 **Methods**

29 This work was performed in accordance with the guidelines of the Cochrane Collaboration and
30 Preferred Reporting Items for Systematic review and Meta-analysis Protocols (PRISMA) [3,4]. The
31 protocol is registered in PROSPERO. Registration number: CRD42018110118.

32 This review was a part of a larger guideline on Menière's disease which was published by the
33 Danish Health Authorities in 2018.

34

35 *Literature search*

36 We performed a systematic literature search in two steps. Initially, we identified systematic reviews
37 that, in accordance to our inclusion criteria, investigated the use of endolymphatic sac surgery in
38 Menière's disease. The search for systematic reviews was performed on December 19th, 2017, with
39 no restrictions regarding date of publication. Subsequently, we performed a search to identify
40 individual randomized controlled trials (RCTs). The search for RCTs was performed February 2nd
41 2018, and was limited to the publication dates of the latest search in the identified systematic
42 reviews (which in this case was November 2012). The search for individual RCTs was limited to
43 the search date of the Cochrane review, as the search strategy and inclusion criteria of the Cochrane
44 review was identical to that of the current manuscript. As such, the thorough and well-performed
45 literature search performed in the Cochrane review served as a foundation, from which the authors
46 of the current review performed an updated literature search All searches were performed in the
47 databases EMBASE, MEDLINE, and PsycINFO via Ovid (Wolters Kluwer, Aalphen aan der Rijn,
48 the Netherlands). The search strategy was developed using medical subject heading terms (MeSH)

49 and text words related to our eligibility criteria, i.e. Meniere, Menieres, Meniere disease/syndrome
50 (English), Menieres sygdom/syndrome (Danish), menieres sykdom (Norwegian), Menieres sjukdom
51 (Swedish). There were no restrictions in regard to publication status, however, the search was
52 limited to literature written in English, Danish, Norwegian and Swedish. Search protocols are
53 provided in the supplementary material section.

54

55 ***Study selection:***

56 The results of the search for systematic reviews and individual RCTs were imported to RefWorks
57 (Proquest, Ann Arbor Michigan, USA). Subsequently, duplicate references were removed and the
58 remaining records were imported into Covidence software (Covidence, Melbourne Australia) for
59 literature screening and data management. Titles and abstracts of potential studies was screened by
60 one reviewer (LD) to assess if the inclusion criteria were met. The initial selection of studies was
61 assessed by an additional reviewer (HEC). Subsequently, the full text of potential studies was
62 screened independently by two review authors (LD and JHS) for eligibility. Disagreement was
63 resolved through discussion or by consultation of a third reviewer (HEC). Neither of the review
64 authors were blinded in regard to journal titles, study authors/institutions or year of publication. A
65 PRISMA flow chart [5] was created and used to document the number of studies identified.

66 The selection of studies was based on the Population, Intervention, Comparison and Outcome
67 (PICO) framework [6] with the following structure: **Population:** *Inclusion* criteria were age 18 or
68 above, and a diagnosis of definite or probably Menière's disease as defined by Bárány Society 2015
69 [2] or the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) criteria
70 from 1995 [7]. Bárány Society diagnostic criteria for definite Menière's disease include: A) Two or
71 more spontaneous episodes with dizziness, each lasting between 20 minutes and 12 hours. B) At
72 least one hearing test showing low to medium frequency sensorineural hearing loss on the affected

73 ear before, during or after a dizziness episode. C) Fluctuating symptoms of the affected ear in the
74 form of tinnitus, hearing loss or increased volume / pressure. D) Symptoms cannot be explained
75 better by another diagnosis. Partially, the diagnostic criteria for probable Menière's disease include
76 the same criteria (A, C, D), but no evidence of a continuing or fluctuating sensorineural hearing loss
77 is required. *Exclusion* criteria were patients with a diagnosis of vertigo other than Menière's disease
78 and patients with Ménière's syndrome that did not fulfill the appropriate criteria as described above.

79 **Intervention and Comparison:** We included randomized controlled studies investigating the usage
80 of endolymphatic sac surgery compared to patients that did not receive endolymphatic sac surgery.

81 **Outcome:** The primary outcomes included the frequency of vertigo attack(s) and serious adverse
82 events as assessed at a minimum of three month following initial treatment. Secondary outcomes
83 included; hearing loss, reduction of tinnitus, quality of life, impact on daily life, vestibular function,
84 frequency and length of vertiginous attacks, severity of the attacks and patient-reported operative
85 effect. Tinnitus and duration of the vertiginous attacks were investigated three months after
86 initiating of the intervention. The remaining secondary outcomes were evaluated at the longest
87 follow-up (minimum one year after the intervention). Frequency and duration of vertiginous attacks
88 at longest follow-up (minimum one year after the intervention) were included as a secondary
89 outcome measure.

90

91 ***Quality assessment and data extraction***

92 The quality of the included systematic review was assessed using the AMSTAR tool [8]. The
93 AMSTAR evaluation was performed to ensure methodological rigidity of the review, from which
94 the second literature search for individual RCTs was based upon. The quality of individual RCTs
95 was evaluated using the Cochrane risk of bias tool which included the following characteristics:
96 Randomization sequence generation; Treatment allocation concealment; Blinding of patients and

97 personnel; Blinding of outcome assessors; Completeness of outcome data; Selective outcome
98 reporting; Other sources of bias. Following a combined assessment of the results reported in the
99 included studies, the certainty of effect on the individual outcomes was evaluated using the GRADE
100 approach [9]. Results from RCT studies are by default considered to be of high quality, yet the
101 quality may be downgraded to either moderate, low or very low based upon the following domains:
102 overall risk of bias; inconsistency; indirectness; imprecision and publication bias. The overall
103 quality of evidence was subsequently based upon the lowest quality of the primary outcome in
104 accordance to the GRADE approach.

105

106 Two review authors (LD and HEC) independently performed the quality assessment and subsequent
107 data extraction. Data extraction included population demographics, baseline characteristics, details
108 on intervention and control conditions, study design, outcome, and time of measurement.

109 All data was exported to Review Manager (version 5.2) (Informer Technologies Inc) and any
110 potential discrepancies were resolved through discussion.

111

112 *Statistical analysis*

113 Due to a heterogenic reporting style and inconsistent reporting of primary data in the identified
114 studies, it was not possible to perform any data-analysis or summary of findings. As such, the effect
115 estimates for the individual outcome and overall quality of the evidence were solely narratively
116 described. Authors of the included studies were not contacted for further information.

117

118

119 **Results**

120 In the search for systematic reviews, we identified 87 references. Following removal of duplicates
121 and none-relevant references, we identified seven systematic reviews [10-16] that we obtained in
122 full text and read thoroughly. Of these, one systematic Cochrane review [15], which included three
123 relevant RCTs, matched our clinical question,. A search for further RCTs based on the search date
124 from the Cochrane review (which was November 2012) [15] identified 57 references. Following the
125 screening and selection process, there were no RCTs published after the search date from the
126 Cochrane review, that matched the inclusion criteria. The total amount of evidence in this review is
127 based on three RCT with a total of number of 59 patients [17-19]. A flowchart can be seen in figure
128 1.

129

130 ***The included studies:***

131 The populations in the included studies were described as classical Menière's disease patients
132 without specification of the diagnostic criteria applied. Thomsen et al., (1981) [19] compared
133 endolymphatic shunt surgery with mastoidectomy in 30 patients refractory to medical treatment. All
134 patients filled out a dizziness related questionnaire (frequency, duration, and severity of attacks) as
135 well as a registration of their self-perceived symptoms of vertigo, tinnitus, and hearing impairment
136 on a scale ranging from zero to three (higher scores indicative of more severe symptoms). These
137 measurements were performed three months prior to and 12 months following surgery. At the end
138 of the trial, patients were asked about their subjective evaluation of the effect and a pure tone
139 audiometry (PTA) was performed. The study by Bretlau et al., (1989) [17] consisted of a nine-year
140 follow-up of the study by Thomsen et al., (1981) [19] In this follow-up study, 23 patients from
141 Thomsen et al., (1981) [19] participated. Patients were once again asked about their subjective
142 evaluation of the surgical effect and a PTA was performed. The study from Thomsen et al., (1998)

143 [18] compared endolymphatic shunt surgery with insertion of ventilation tubes in 29 patients
144 refractory to medical treatment. On a daily basis, the patients registered frequency and severity of
145 vertiginous attacks six months pre-surgery and 12 months following surgery. Patients were
146 interviewed about their subjective symptoms and a PTA audiogram was performed.

147

148 *Frequency of vertigo attacks*

149 In the study by Thomsen et al., (1998) [18] there was a general improvement in patient-reported
150 vertigo scores following surgery both in the active group and in the control group when compared
151 to preoperative conditions ($p < 0.01$, no primary data provided). When treatment groups were
152 compared, patients in the placebo group had a slightly worse vertigo score following surgery
153 compared to the active group ($p < 0.05$, no primary data provided). In the nine-year follow-up by
154 Bretlau et al., (1989) [17] only one patient in the active group continued to have periodic attacks,
155 whereas no patients in the placebo group had any recurrent attacks. There continued to be no
156 difference between the two treatment groups (no data or statistical analysis provided). In another
157 study by Thomsen et al., (1998) [17], there was a reduction in the number of dizzy spells in both
158 groups following endolymphatic shunt surgery and insertion of ventilation tube, with approximately
159 30 percent of patients in both groups having no attacks following surgery. There were no significant
160 differences between the two treatment groups (no primary data provided).

161

162 *Reduction in tinnitus*

163 In the study by Thomsen et al., (1981) [19], an improvement in patient-reported tinnitus was
164 observed in the active group following surgery when comparing to preoperative conditions. There
165 was no difference between the active group and the placebo group (no primary data or statistical

166 analysis provided). In Thomsen et al., (1998) [17], there was no significant effect on tinnitus in
167 neither the placebo group nor the shunt surgery group (no primary data provided, $p>0.05$).

168

169 ***Impact on daily life***

170 Following surgery, in terms of functionality, Thomsen et al., (1981) [19] reported a significant
171 reduction in disease severity in both groups when assessed by investigators' global score (no
172 primary data provided, $p<0.005$). There was, however, no differences in disease severity between
173 the placebo group and the active groups (no primary data or statistical analysis provided). In
174 correlation, Thomsen et al. 1998 [18] reported an improved level of functionality in both groups
175 following surgery (no primary data provided, $p<0.05$), with no difference between the two groups
176 (no primary data provided).

177

178 ***Hearing loss***

179 At the end of the trial, Thomsen et al., (1981) [19] found no significant differences between the
180 placebo group and the active group in regard to average mean values of 250, 500 and 1000 Hz, as
181 measured by pure tone audiometry (PTA) (no primary data or statistical analysis provided). In the
182 nine-year follow-up from Bretlau et al. (1989) [17], there continued to be non-significant inter-
183 group difference between mean values measured by PTA (no primary data or statistical analysis
184 provided). In the study by Thomsen et al., (1998) [18], there was no significant differences in PTA
185 between groups, neither before surgery (sac shunt: 55dB (23-86); ventilation tube: 54db (8-71),
186 median (range)) nor 12 months following surgery (sac shunt: 55 (26-anacusis); ventilation tube 48
187 (5-79), median range) ($p>0.05$).

188

189 ***Patient-reported operative effect***

190 In Thomsen et al. (1981) [19], both groups reported positive operative effect as compared to pre-
191 surgery (73% active group; 67% placebo group), with no significant differences between the two
192 groups (no analysis provided). In the nine-year follow-up study by Bretlau et al., (1989), 70 % of
193 the patients in both groups continued to consider their surgery successful (no analysis provided). In
194 Thomsen et al., (1998), 86% of patients receiving ventilation tube and 60% receiving
195 endolymphatic shunt surgery, reported a favorable effect of the intervention. There were no
196 significant differences between the two groups ($p>0.05$).

197

198 None of the studies reported on serious adverse events, quality of life, length of vertigo attack or
199 vestibular function.

200

201 *Quality of evidence*

202 The AMSTAR evaluation of the included systematic review showed that this review had an
203 adequate description of all necessary domains, and thus was considered of high quality.

204 The assessment of the individual RCTs by the Cochrane Risk of bias tool, showed that in all three
205 studies the random sequence generation and allocation concealment was unclear and there was a
206 high risk of other biases due to inadequate reporting of primary data and statistical analysis.

207 Subsequent rating of the overall certainty of effect was very low for all outcomes due to serious
208 imprecision and serious risk of bias. An overview of the AMSTAR evaluation and the Cochrane
209 risk of bias can be found in the figures 2 and 3.

210

211 **Discussion**

212 The objective was to provide an overview and quality assessment of the current evidence regarding
213 the use of endolymphatic sac surgery in patients with definite and probable Menière's disease. Our

214 findings showed that, despite surgery being applied to treat Meniere disease since 1927, the amount
215 of well-performed RCTs on the matter continues to be scarce. Of the identified literature, only three
216 RCTs were found compatible with the inclusion criteria of this particular review. All studies
217 investigated the use of endolymphatic sac surgery, but one of the RCT studies was a nine-year
218 follow-up on the patients from one of the other RCTs. The included RCTs were identified in one
219 high quality Cochrane review as assessed by the AMSTAR tool. An updated literature search
220 showed that no further relevant RCTs have been published since the search applied in the
221 systematic review. As assessed by the Cochrane risk of bias tool, the quality of the included RCTs
222 was poor, with inadequate reporting of primary data and underlying statistical analysis, in addition
223 to the inclusion of few patients and other substantial methodological flaws. In accordance, the
224 overall certainty of the effect on the predefined outcomes, as assessed by the GRADE approach,
225 was very low. Due to a severe lack in the reporting of primary data in all three studies, it was not
226 possible to perform any combined analysis and thus to identify any common effects of this
227 intervention. All three studies, however, individually reported of an improvement in symptoms in
228 both groups after surgery when compared with preoperative conditions. This included an
229 improvement in vertigo, impact on daily life and in patient-reported operative effect. When the
230 placebo and active groups were compared, there were no significant differences in treatment effects
231 for these above-mentioned outcomes. In accordance to the findings within the included studies,
232 these findings may indicate a substantial placebo effect following surgery for Menière's disease, yet
233 it may also to some extent reflect the natural disease progression found in Menières disease.
234 It is important to include a suspected non-effective placebo treatment in studies on surgical
235 procedures in Menières disease. A recent study by Saliba et al. 2015 [20] compared endolymphatic
236 sac decompression with endolymphatic duct blockage in a randomized non-blinded design. . This
237 study compared two procedures related to the endolymphatic sac and was therefore not included in

238 the present study. The study has an important risk of bias due to non-blinded design towards the
239 patients and the observers, which might have biased the conclusions even though endolymphatic
240 duct blockage was proven to be superior in vertigo control compared to endolymphatic sac
241 decompression. Thus, it is important that the new surgical procedure of endolymphatic duct
242 blockage is compared to a suspected non-effective placebo sham surgery in blinded design towards
243 patients and observers conducting the clinical examinations.

244 The well-known placebo effect in Menière's disease, as well as the natural progression of this
245 disease, serve as potentially serious confounders when seeking to evaluate treatment effects, and
246 thus there is a need for large, well-performed RCT studies. We chose not to include non-
247 randomized trials in this review, because these types of studies would not sufficiently directly
248 address our research question, in addition to the high risk of bias in these types of study designs.

249 That being said, a review by Lim et al., (2015) [12], who included observational studies, also failed
250 to substantiate the efficacy of this treatment in Menière's disease and subsequently pointed towards
251 the need for better research.

252 As such, based on the current evidence, it is not possible to conclude whether endolymphatic
253 surgery in Menière's disease yields any positive results aside from a potential placebo effect. This is
254 in line with the conclusions of other systematic reviews previously published on this matter [12,15].

255 Nevertheless, based on expert opinions, this treatment is still, in some cases, considered a good
256 treatment option for Menière's disease [11]. Given the fact that this is an invasive treatment, there is
257 a high demand for well-performed studies that indeed show that the potential benefits following
258 surgery exceeds the potential side effects.

259

260 ***Strength and limitations of the current study***

261 This systematic review was performed using a transparent method and a priori defined criteria. This
262 included a protocol registration, a systematic literature search, duplicate study selection, quality
263 assessment, and data extraction. Limitations include a restricted search in study design and
264 language. The results mentioned in this review are solely based upon the published data, as authors
265 of the included studies were not contacted for further information.

266

267 **Disclosure of interest**

268 The authors report no conflict of interest.

269

270 **Conclusion**

271 Given that endolymphatic sac surgery is an invasive procedure, there should be a demand for good
272 evidence evaluating its potential beneficial effects and associated risks. However, until now there is
273 still a lack of high quality research underlining the fact that endolymphatic sac surgery may provide
274 significant and adequate symptomatic relief for patients diagnosed with Menière's disease.

275 **References**

- 276 1. Nakashima T, Pyykkö I, Arroll MA, et al. Meniere's disease. *Nature reviews Disease*
277 *primers*. 2016 May 12;2:16028.
- 278 2. Lopez-Escamez JA, Carey J, Chung WH, et al. Diagnostic criteria for Meniere's disease.
279 *Journal of vestibular research : equilibrium & orientation*. 2015;25(1):1-7.
- 280 3. Furlan AD, Malmivaara A, Chou R, et al. 2015 Updated Method Guideline for Systematic
281 *Reviews in the Cochrane Back and Neck Group*. *Spine*. 2015 Nov;40(21):1660-73.
- 282 4. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and
283 *meta-analysis protocols (PRISMA-P) 2015 statement*. *Systematic reviews*. 2015 Jan 1;4:1.
- 284 5. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic
285 *reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and*
286 *elaboration*. *BMJ (Clinical research ed)*. 2009 Jul 21;339:b2700.
- 287 6. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 2. Framing the question and
288 *deciding on important outcomes*. *Journal of clinical epidemiology*. 2011 Apr;64(4):395-400.
- 289 7. Committee on Hearing and Equilibrium guidelines for the diagnosis and evaluation of
290 *therapy in Meniere's disease*. American Academy of Otolaryngology-Head and Neck
291 *Foundation, Inc. Otolaryngology--head and neck surgery : official journal of American*
292 *Academy of Otolaryngology-Head and Neck Surgery*. 1995 Sep;113(3):181-5.
- 293 8. Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to
294 *assess the methodological quality of systematic reviews*. *BMC medical research*
295 *methodology*. 2007 Feb 15;7:10.
- 296 9. Guyatt GH, Oxman AD, Schunemann HJ, et al. GRADE guidelines: a new series of articles
297 *in the Journal of Clinical Epidemiology*. *Journal of clinical epidemiology*. 2011
298 *Apr;64(4):380-2*.

- 299 10. Dickins JR, Graham SS. Meniere's disease--1983-1989. *The American journal of otology*.
300 1990 Jan;11(1):51-65.
- 301 11. Flores Garcia ML, Llata Segura C, Cisneros Lesser JC, et al. Endolymphatic Sac Surgery for
302 Meniere's Disease - Current Opinion and Literature Review. *International archives of*
303 *otorhinolaryngology*. 2017 Apr;21(2):179-183.
- 304 12. Lim MY, Zhang M, Yuen HW, et al. Current evidence for endolymphatic sac surgery in the
305 treatment of Meniere's disease: a systematic review. *Singapore medical journal*. 2015
306 Nov;56(11):593-8.
- 307 13. Pender DJ. Endolymphatic hydrops and Meniere's disease: a lesion meta-analysis. *The*
308 *Journal of laryngology and otology*. 2014 Oct;128(10):859-65.
- 309 14. Pullens B, Giard JL, Verschuur HP, et al. Surgery for Meniere's disease. *The Cochrane*
310 *database of systematic reviews*. 2010 Jan 20(1):Cd005395.
- 311 15. Pullens B, Verschuur HP, van Benthem PP. Surgery for Meniere's disease. *The Cochrane*
312 *database of systematic reviews*. 2013 Feb 28(2):Cd005395.
- 313 16. Sood AJ, Lambert PR, Nguyen SA, et al. Endolymphatic sac surgery for Meniere's disease:
314 a systematic review and meta-analysis. *Otology & neurotology : official publication of the*
315 *American Otological Society, American Neurotology Society [and] European Academy of*
316 *Otology and Neurotology*. 2014 Jul;35(6):1033-45.
- 317 17. Bretlau P, Thomsen J, Tos M, et al. Placebo effect in surgery for Meniere's disease: nine-
318 year follow-up. *The American journal of otology*. 1989 Jul;10(4):259-61.
- 319 18. Thomsen J, Bonding P, Becker B, et al. The non-specific effect of endolymphatic sac
320 surgery in treatment of Meniere's disease: a prospective, randomized controlled study
321 comparing "classic" endolymphatic sac surgery with the insertion of a ventilating tube in the
322 tympanic membrane. *Acta oto-laryngologica*. 1998 Nov;118(6):769-73.

- 323 19. Thomsen J, Bretlau P, Tos M, et al. Placebo effect in surgery for Meniere's disease. A
324 double-blind, placebo-controlled study on endolymphatic sac shunt surgery. Archives of
325 otolaryngology (Chicago, Ill : 1960). 1981 May;107(5):271-7.
- 326 20. Saliba I, Gabra N, Alzahrani M, et al. Endolymphatic duct blockage: a randomized
327 controlled trial of a novel surgical technique for Meniere's disease treatment.
328 Otolaryngology--head and neck surgery : official journal of American Academy of
329 Otolaryngology-Head and Neck Surgery. 2015 Jan;152(1):122-9.

330

331

332 **Figure legends**

333

334 **Figure 1:**

335 Flowcharts showing the inclusion and exclusion of systematic reviews and primary studies

336

337 **Figure 2:**

338 Assessment of the methodological quality of the included systematic reviews (AMSTAR). The
339 different domains are presented in the top row. The individual studies are shown in the left column.

340

341 **Figure 3:**

342 Risk of bias assessment as assessed by the Cochrane risk of bias tool. A plus (+) indicates low risk
343 of bias; a question mark (?) indicates unclear risk of bias and a minus (-) indicates high risk of bias.
344 The specific type of bias is presented in the top column, and the individual studies in the left row.

345