Curr Otorhinolaryngol Rep (2014) 2:137–143
DOI 10.1007/s40136-014-0055-8

Intratympanic Therapies for Menière's Disease

Matthew W. Miller · Yuri Agrawal

Published online: 1 July 2014

Abstract There are multiple treatment options to consider when managing patients with Menière's disease. When conservative measures fail to control symptoms of Menière's disease, escalation of interventions may be required. Targeted drug delivery to the round window with intratympanic injections allows for local application of high concentrations of medications, largely avoiding systemic side effects. Intratympanic steroids (ITS) have been shown to be effective at controlling vertigo symptoms, with less robust control rates than those seen with the use of intratympanic gentamicin. Dosing strategies have been modified over time to limit the potential for intratympanic gentamicin-induced ototoxicity. The introduction of ITS coupled to a polymer designed for sustained round window drug application, may potentially afford improved duration of symptom control. This review evaluates the recent literature over the last year involving intratympanic therapies for Meniere's disease.

Keywords Meniere's disease · Intratympanic · Transtympanic · Dexamethasone · Methylprednisolone · Gentamicin · Therapy · Treatment · Endolymphatic sac surgery · Steroid

M. W. Miller
Division of Otology, Neurotology, and Skull Base Surgery, Department of Otolaryngology-Head and Neck Surgery, The Johns Hopkins University School of Medicine, 601 N. Caroline St., 6th Fl. JHOC 6240, Baltimore, MD 21287, USA
e-mail: mmill168@jhmi.edu

Y. Agrawal (✉)
Division of Otology, Neurotology and Skull Base Surgery, Department of Otolaryngology-Head and Neck Surgery, The Johns Hopkins University School of Medicine, 550 N Broadway, Ste 1100, Baltimore, MD 21205, USA
e-mail: yagrawa1@jhmi.edu

Introduction

Prosper Menière originally described the constellation of symptoms of episodic vertigo, aural fullness or tinnitus, and hearing loss in 1861. Although Menière's disease is considered idiopathic, symptoms are attributed to excess endolymph production or impaired reabsorption, leading to the pathologic condition of endolymphatic hydrops. Schuknecht proposed that membranous ruptures lead to leakage of endolymph into the perilymph and altered functioning of the cochlear and vestibular sensory epithelia, resulting in Menière's attacks [1]. When conservative measures such as low-sodium diet and use of diuretics and/or betahistine fail to control symptoms, additional interventions may be required. Targeted drug delivery to the round window with intratympanic injections allows for local application of high concentrations of medications and largely avoids systemic side effects. Although intratympanic injections of a variety of medications (gentamicin, streptomycin, steroids, ganciclovir, hyaluronic acid, lidocaine, and latanoprost) for treatment of Menière's disease have been performed, the use of intratympanic gentamicin (ITG) or intratympanic steroids (ITS) is the most common. The purpose of this article is to review recently published studies over the last 12 months that have used intratympanic drug delivery strategies for the treatment of Menière's disease.

A PubMed search was performed using a combination of the keywords: intratympanic and Menière's disease; intratympanic and Menière's disease and gentamicin; Menière's disease and steroid; Menière's disease and dexamethasone; and Menière's disease and methylprednisolone. Nine studies involving the intratympanic delivery of medications to the round window in human subjects over the preceding 12 ± 2 months were reviewed, and data

from eight are included in Table 1. Three studies reported on the use of ITG alone [2•, 3•, 4•]. One of the studies was a case report and was not included [5•]. Two studies involved the use of intratympanic dexamethasone (ITD) as monotherapy [6•, 7•]. Two studies involved the comparison of two treatment modalities [8•, 9•]. Although it fell outside the period intended for review, the study by Lambert et al. in 2012 [10•] was included because of its study design and introduction of a new medication for intratympanic delivery. Study designs are included in Table 1 and will be reviewed further with discussion of the individual articles below.

All published studies reviewed (with the exception of one-Wasson et al. [4•]) used the American Academy of Otolaryngology-Head and Neck Surgery Menière's Disease guidelines for diagnosis and evaluation of treatment published in 1995 [11]. Patients were classified with the diagnosis of "definite Menière's Disease" based on the following

(1) Two or more definitive spontaneous episodes of vertigo 20 min or longer
(2) Audiometrically documented hearing loss on at least one occasion
(3) Tinnitus or aural fullness in the treated ear
(4) Other causes excluded

With respect to evaluating therapies in Menière's disease, the AAO-HNS guidelines recommend evaluating one treatment course at a time. The guidelines establish several classes of vertigo control, with vertigo defined as a sensation of motion when no motion is occurring. The class of vertigo control is based on a numerical value of $(X/Y) \times 100$, where $X =$ the number of episodes per month between 18 and 24 months after treatment, and $Y =$ the number of episodes per month over the 6 months prior to treatment. Most groups consider class A (complete) or class B (=1–40 or substantial) as attaining good control of symptoms. Though the guidelines list class A-F, studies most often report classes A and B. For the purposes of this review, the term "vertigo control" will include patients in class A and B.

Audiometric data were reported in studies using a 4-frequency PTA (0.5, 1, 2, and 3 kHz [2•, 6•, 7•] or 0.5, 1, 2, and 4 kHz [3•, 4•, 8•]). One study reported mean hearing thresholds at several frequencies [9•] and another does not report specific hearing outcomes data [10•]. Pre- and post-treatment testing methods varied, including the use of electrocochleography (ECoG), videonystagmography, caloric testing, and cervical vestibular-evoked myogenic potential (cVEMP). Additional outcome measures included the use of some of the following: Dizziness Handicap Inventory (DHI), Tinnitus Handicap Inventory (THI), 40-item Menière's disease specific quality of life (QOL) questionnaire, Menière's disease Patient-Oriented Symptom-Severity Index (MDPOSI), and Gates' vertigo scale.

Intratympanic Steroid Injection

ITS injections for control of Menière's disease symptoms were initially suggested by Sakata et al. in 1987 and positive effects further described in 1991 [12]. The proposed mechanism of action is the effect on immune suppression and ion homeostasis [13]. ITS allow for the use of higher concentrations and avoidance of systemic side effects [14]. Intratympanic delivery is shown to down-regulate pro-inflammatory cytokines in animal models [13]. Glucocorticoids also have a role in ion homeostasis with binding to the mineralocorticoid receptor [15]. The induction of mineralocorticoid receptor-mediated genes, such as synthesis of Na^+, K^+-ATPase, helps to regulate stria vascularis function and maintenance of the endocochlear potential [13]. Dexamethasone has also shown increased absorption from the endolymph compared to methylprednisolone following intratympanic injection in an animal model. Though methylprednisolone concentrations are higher in sampled endolymph, it is thought that this is due to decreased absorption by cochlear and vestibular tissues. Recent studies most often report the use of dexamethasone for intratympanic injection. A review of 13 studies involving the use of ITS for Menière's disease was performed by Hu and Parnes in 2009 [16]. A meta-analysis could not be performed due to the heterogeneity of the data. Dexamethasone of varying concentrations (1–16 mg/mL) was used in 12/13 studies, and methylprednisolone (80 mg/mL) was used in the remaining study. Of the 13 studies, 8 were considered positive (beneficial effect of steroids) and 5 negative (no benefit). Only 2 of the studies were randomized, controlled studies, and had small sample sizes of $N = 20$ and $N = 22$ [17, 18]. The majority of studies (9/13) reviewed were retrospective. Similarly, a Cochrane review in 2011 only identified a single randomized control trial, with a low risk of bias, which demonstrated a benefit for use of ITS in treating Menière's disease [19]. Due to the heterogeneous nature of studies, additional research into the effectiveness of ITS is necessary.

Of the literature published over approximately the last year, two studies involving the use of ITS warrant additional, more in-depth discussion [7•, 10•]. Martin-Sanz et al. [7•] were the first to report results of a prospective study utilizing ECoG to monitor response to ITS therapy in patients. Patients with unilateral definite Menière's disease were administered 3 weekly ITD (4 mg/mL) injections according to a schedule that was deemed as effective as 3 consecutive daily injections by the same group (see

Table 1 Study characteristics

Study (first author)	Level of evidence	Drug	Conc. mg/mL	Treatment protocol	AAO-HNS 1995-defined MD	Outcome measures	Follow-up	Sample (no.)	Vertigo control (class A+B; at 2 years)	Mean change in PTA (dB)
Casani [2•]	IV	ITG	26.7	LD—injections with 20-day interval (1–2 injections) HD—twice daily every 6 days, 6 total injections	+	FLS, vertigo control, PTA, SDS, disequilibrium	1 month; 1, 2 years	LD—42 HD—35	LD—90 % HD—94 %	LD—5.9 HD—15.6
Quaglieri [3•]	IV	ITG	26.7	Injections with minimum 1 month interval	+	Vertigo control, PTA, SDS, cVEMP	1, 3, 6, 12 months, then yearly	174	96.5 %	13
Wasson [4•]	IV	ITG	26	3 times daily for 4 days	−	Vertigo control, PTA, calorics	2 years, >15 years	9*	100 %	3.7
Gabra [8•]	III	ITG or ITMP	26.7 62.5	3 weekly injections	+	Vertigo control, aural fullness, tinnitus, PTA, SDS	6, 12 month	42 45	82.9 % class A at 1 year 48.1 % class A at 1 year	−6.6 7.6
Paradis [9•]	III	ITG N/A	26.7	4 weekly injections, unless controlled after 3rd Endolymphatic sac surgery	+	Hearing stage, vertigo control, QOL, PTA	2 years	37 30	87 % 63 %	−1.2 12
Martin-Sanz [6•]	III	ITD	4	3 daily injections or 3 weekly injections	+	Vertigo control, PTA, calorics	2 years	22 34	59.1 %	2.6 2.1
Martin-Sanz [7•]	III	ITD	4	3 weekly injections	+	Vertigo control, ECoG	3, 6, 9, 12 months; 2 years	53	60.4 % at 1 year and 32.1 % at 2 years	1.2 at 1 year
Lambert [10•]	I	ITD	Placebo 3 12	Single injection	+	Vertigo frequency (IVRS), THI, MDPOSI, Gates' vertigo score	1, 2, 3 months	14 14 16	See text	NR

ITG intratympanic gentamicin, *ITMP* intratympanic methylprednisolone, *ITD* intratympanic dexamethasone, *LD* low-dose, *HD* high-dose, *FLS* functional level score, *PTA* pure tone average, *SDS* speech discrimination score, *cVEMP* cervical vestibular-evoked myogenic potential, *QOL* quality of life, *ECoG* electrocochleography, *IVRS* interactive voice-response system, *THI* tinnitus handicap inventory, *MDPOSI* meniere's disease patient-oriented symptom-severity index, *NR* not reported

* 9/16 patients contacted via telephone >15 years after initial treatment

Table 1) [6•]. ECoG was obtained immediately prior to injection and 1 month following the last injection. A significant decrease was seen in the proportion of individuals with an SP/AP ratio >0.5 before (77.35 %) vs after (16.98 %) steroid therapy. Pre-treatment DHI scores are provided, but no post-treatment scores were available for comparison. Patients experiencing a larger reduction (>0.5) in pre- and post-treatment SP/AP ratio tended to have better complete vertigo control, but this did not reach statistical significance. The study had several limitations. The reports of vertigo control are limited due to recall bias, with reporting of vertigo every 3 months. The time course of the recurrence of an abnormal ECoG response in this study population is unknown beyond 1 month after steroid injection. Also, the 2-year vertigo control is almost 50 % less than that reported in their retrospective study (32.1 vs 58.8 %) published in the same year [6•]. The study demonstrates a potential physiologic effect of ITS administration at the level of the cochlea in short-term follow-up.

With multiple studies, suggesting benefit of ITS therapy for symptom control in Menière's disease, a randomized, double-blind, placebo-controlled, dose-escalation phase Ib study reported the use of a sustained delivery method [10•]. The authors cite the use of aqueous formulations may have limited and variable exposure to the round window and inner ear tissues. This study was intended to determine the safety of OTO-104 use in patients. OTO-104 is a suspension of dexamethasone in a glycol polymer called poloxamer. The polymer solidifies at body temperature, following intratympanic delivery with a 26-gu. needle. The suspension is meant for sustained steroid delivery at the round window. Early on in the study, patients were randomized to placebo or 3 mg of OTO-104. Following a blinded review of accumulated data demonstrating no safety concerns for 3 mg of OTO-104, the use of high-dose (12 mg) OTO-104 was opened to enrollment. Rigorous data collection methods were used, including daily reporting of vertigo symptoms using an interactive voice response system (IVRS). Inclusion criteria were

(1) 2 or more episodes of vertigo per month for 2 months before the study lead-in period
(2) 2 or more episodes of definitive vertigo during the 4-week lead-in period
(3) A history of Menière's disease for <20 years
(4) Asymmetric, low-frequency, sensorineural hearing loss (min of 25 dB decrement at 250 Hz)
(5) A history of using low-salt diet and/or diuretics for 1 month of longer without relief

Outcomes were reported including treatment-emergent adverse events, THI and MDPOSI scores, change in vertigo frequency, laboratory measurements, vital signs, and ECG. A total of 44 patients were included and randomized. The most notable adverse treatment event was tympanic membrane perforation, occurring in 14 % of the 3-mg OTO-104, 38 % of 12-mg OTO-104 groups, and 0 % of placebo patients. All but 1 of the 8 total perforations closed without intervention by the end of the study. THI scores trended down in the 3 and 12-mg OTO-104 groups at 3 months and approached a significant difference relative to placebo. There was a persistent decrease in the vertigo frequency in patients receiving 12 mg of OTO-104 compared to the placebo and 3-mg OTO-104 groups over the study period, but this was not statistically significant. The mean change in vertigo frequency for patients in the 12-mg group from baseline to month 3 was −0.211 or ∼6 episodic days per month. This represents a 70 % reduction in frequency compared to the change seen in the placebo group (−0.124 or ∼3.5 episodic days per month).

Benefits of the study design include limiting symptom recall to 1 day prior to reporting and randomization with inclusion of a placebo control group. Another strength of the study design included a lead-in period, requiring patients to demonstrate the ability to report symptoms using the IVRS, and eliminating those unable to comply with the data collection methods. The authors suggest additional benefits which include eliminating the need for a second ventilation hole, minimizing post-injection sequelae (i.e., vertigo), and allowing patients to sit upright immediately. The inability to detect a significant difference in the treatment regimens may be due to the small sample size. A larger randomized, double-blind, placebo-controlled clinical trial is currently underway that is intended to have greater statistical power.

Intratympanic Gentamicin Injection

Originally, Schuknecht described the use of intratympanic streptomycin for its vestibulotoxic effects to manage Menière's symptoms [20]. Later, Lange described the use of ITG therapy for its effects on sensory hair cell death and possible effects on the dark cells that are responsible for endolymph production [21]. ITG has been shown to concentrate in type I hair cells in tissues harvested 1 week after injection in an animal model [22]. There was a subsequent 68 % loss of vestibular sensory hair cells in tissues harvested at 3 weeks, with losses greater in type I relative to type II vestibular hair cells.

A variety of ITG dosing strategies for Menière's disease have been described over the years and recently reviewed in a meta-analysis by Huon et al. [23•]. They included 12 prospective and 2 randomized controlled studies in their analyses. Dosing strategies reviewed included fixed or titration schedules, with a range of gentamicin concentrations from 12 to 80 mg/mL. There were no studies that

included daily dosing. With a review of 14 studies published over a 16-year period, patients (pooled $N = 599$) required an average number of 2.1 treatments to achieve 87.5 % rate of substantial control.

There has been a trend toward the use of lower dose strategies in the recent years. Although lower doses may require repeat injections to obtain control, these have shown to have relatively limited impact on residual hearing. This dosing strategy was further reinforced by two retrospective studies published in the last year [2•, 3•]. One group [2•] compared an "on-demand" dosing schedule with a higher dosing schedule and was able to obtain similar rates of vertigo control. Not only were hearing outcomes better in the low-dose group, but patients also experienced significantly less post-treatment disequilibrium. Another group reported results of a similar dosing regimen, also demonstrating high vertigo control rates (96.5 %) [3•]. They treated 180 patients with low-dose gentamicin (26.7 mg/mL) using an "on-request" regimen and a minimum treatment interval of 1 month. A single injection provided effective long-term control in 40.2 % of patients, and multiple injections were required to achieve the same level of control in an additional 43.7 %. There was a small group of 22 patients (12.6 %) that required additional injections after >2 years of complete vertigo control. When evaluating changes in PTA, cVEMP, and caloric responses, only a significant reduction in the caloric response was seen.

Intratympanic Gentamicin Injection vs Endolymphatic Sac Surgery

Endolymphatic sac surgery (ESS) for Menière's disease continues to be controversial. In the only study published over the last year to compare a surgical treatment with an intratympanic therapy, a retrospective review of 67 patients that had either ITG therapy or ESS added to the existing controversy regarding the role of ESS in the management of Menière's disease. One surprising finding in the surgically treated group was the high rate of profound deafness (10 %) experienced by patients. Patients also had lower rates of vertigo control compared to the ITG group (63 vs 87 %), and 27 % had to pursue alternative treatment to gain symptom control. The study was limited by its retrospective nature and baseline differences in hearing stage between ITG and ESS groups, which may correlate with a different natural history of the disease (as symptoms tend to "burn out" over time). This study does bring into question the utility of ESS as a hearing-preservation approach, though others have reported high rates of vertigo control (up to 97 % at 15.5 months of mean follow-up) with no significant change in mean PTA [24]. However, even in that study, 30 % of patients did experience at least a 10 dB hearing loss following ESS [24]. The rate of profound hearing loss following surgery was not reported.

Discussion

All studies concluded that there was a benefit of treatment with either ITG or ITS. The use of ITG reported in the above studies provided substantial control in most patients. ITS therapy results in a less robust control of symptoms, most often temporary, but does limit the risk of potential ototoxicity associated with gentamicin use. There was variability in the level of evidence in the reviewed studies, with only one level I study evaluating the efficacy of ITS in symptom control. Most studies were retrospective in design. The use of ITG demonstrates higher rates of vertigo control compared to IT dexamethasone or methylprednisolone, though no randomized studies comparing these treatments head-to-head in comparable patients were performed in these studies. Previous randomized trials have been performed comparing ITG to ITS [18, 25•]. with vertigo control, rates significantly higher in the ITG group compared to ITD in one study (93.8 vs 60.7 %) [25•] and another study reporting no significant difference between the ITG and ITD groups (75 vs 72 %) [18].

Practitioners often site the risk of sensorineural hearing loss as the reason to perform ITS injections over ITG. In the meta-analysis performed by Huan et al., there was a 1.8 % rate of profound hearing loss from IT gentamicin therapy. Pooled mean PTA results did not significantly change following ITG, though the percentage of patients experiencing hearing loss >10 dB (as is often used) was not reported. This is much lower than the 25 % rate of hearing loss >10 dB reported in the meta-analysis by Chia et al., with a profound hearing loss in 6.6 % of patients [26]. The variability in reporting of data in the reviewed studies does make counseling patients on the various treatments somewhat challenging. When comparing treatment strategies, the use of mean change in PTA may not be representative of changes experienced by individuals, with dilution of large individual changes among those with little to no change. The potential for significant hearing loss with ITG exists, and patients should be counseled regarding this risk.

The majority of the reviewed studies used the AAO-HNS guidelines on the diagnosis and evaluation of therapy in Menière's disease. The inherent limitations of the reporting guidelines include limiting patients to one treatment course prior to reporting outcome measures 24 months after treatment. The reporting of vertigo control required comparing the number of definitive vertigo attacks for 6 months prior to therapy to the number of attacks occurring between months 18 and 24 after therapy. This limits the utility of the guidelines for use in cases where the benefit of the treatment, such

as ITS, is known to be temporary and relatively short lived in comparison to ITG or surgical therapies. To circumvent the limitations, some groups use Kaplan–Meier survival curves to report their data, and events are often defined as need for additional injections [2•, 3•, 6•].

Another potential confounder when reporting the treatment of Menière's disease is the possibility of co-existing migraine-associated vertigo. The prevalence of migraine in Menière's disease patients may be up to 56 % [27]. While the studies above report the vertigo control following treatment, whether or not the attacks that occur during the follow-up period are accompanied with the other symptoms of definite Menière's disease is not routinely described. There is potential for confounding with inclusion of migraine-associated vertigo episodes in data sets. Additional limitations of the above studies have been previously described when reviewing other Menière's disease treatments. The natural history of Menière's disease involves resolution over time in up to 71 % of patients [28], reiterating the need for randomized, double-blinded, placebo-controlled studies in order to detect true effects of treatment, and minimize confounding variables.

Conclusion

When patients continue to have symptoms of Menière's disease despite medical management, escalation of therapy may be necessary. In our institution, IT dexamethasone (12 mg/mL) is the preferred modality in patients with serviceable hearing, and dosing is performed on an "as-needed" basis. There are potential side effects, including need for repeat injections, pain, vertigo with injection (can be minimized by bringing solution to body temperature), and tympanic membrane perforation. The results of the OTO-104 trial are encouraging, with potential for improved practice efficiency and patient convenience, as patients will not be required to occupy an exam or treatment room for 30 min following treatment. For individuals with non-serviceable hearing, IT gentamicin (26.7 mg/mL) is administered at 3-week intervals until symptoms are eliminated or controlled to the patient's satisfaction [29]. We feel that this dosing strategy offers an acceptable balance between the potential need for multiple injections and the possibility of the ototoxicity from more aggressive regimens.

Compliance with Ethics Guidelines

Conflict of Interest Matthew W. Miller and Yuri Agrawal declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Recently published papers of particular importance have been highlighted as:
- • Of importance

1. Schuknecht H. Meniere's disease: a correlation of symptomatology and pathology. Laryngoscope. 1963;73:651–65.
2. • Casani AP, Cerchiai N, Navari E, Dallan I, Piaggi P, Sellari-Franceschini S. Intratympanic gentamicin for meniere's disease: short- and long-term follow-up of two regimens of treatment. Otolaryngol Head Neck Surg. 2014;150(5):847–52. *This retrospective study compares the previous higher-dose intratympanic gentamicin regimen with a more recently used lower-dose treatment. High control rates were achieved.*
3. • Quaglieri S, Gatti O, Rebecchi E, Manfrin M, Tinelli C, Mira E, et al. Intratympanic gentamicin treatment "as needed" for meniere's disease. Long-term analysis using the Kaplan–Meier method. Eur Arch Otorhinolaryngol. 2013;271(6):1443–9. *This retrospective study reinforces the notion that patients can be treated with lower doses of intratympanic gentamicin, with repeat doses "as needed" should symptoms persist.*
4. • Wasson J, Upile N, Pfleiderer A. Intratympanic gentamicin treatment for unilateral Ménière's disease: long-term follow up of a proven regime. J Laryngol Otol. 2013;127(1):20–4. *This retrospective review is a follow-up of previously published results. Patients were contacted via telephone to survey ongoing symptom control following a high-dose intratympanic gentamicin protocol.*
5. • Walther LE, Huelse R, Blättner K, Bloching MB, Blödow A. Dynamic change of VOR and otolith function in intratympanic gentamicin treatment for Ménière's disease: case report and review of the literature. Case Rep Otolaryngol. 2013;2013:1–5. *This case report describes the timecourse of the objective changes (video head impulse test, oVEMP, cVEMP, and bithermal calorics) in the weeks following a single dose of intratympanic getamicin.*
6. • Martin Sanz E, Zschaeck C, Christiane ZL, Gonzalez M, Manuel GJ, Mato T, et al. Control of vertigo after intratympanic corticoid therapy for unilateral Ménière's disease: a comparison of weekly versus daily fixed protocols. Otol Neurotol. 2013;34(8):1429–33. *This retrospective study reports no significant difference in vertigo control following a weekly intratympanic dexamethasone protocol compared to a daily protocol.*
7. • Martin-Sanz E, Luzardo CZ, Riesco LR, Patino TM, Sanz R. The use of electrocochleography to monitor the response of Ménière's disease patients to intratympanic steroids. Acta Otolaryngol. 2013;133(11):1158–64. *This is the first prospective study evaluating the effects of intratympanic steroids (dexamethasone) with electrocochleography. The group also reports vertigo control rates using a weekly dosing regimen.*
8. • Gabra N, Saliba I. The effect of intratympanic methylprednisolone and gentamicin injection on Ménière's disease. Otolaryngol Head Neck Surg. 2013;148(4):642–7. *This retrospective study compares vertigo control rates in patients receiving either intratympanic gentamicin or methylprednisolone. Significantly better vertigo control is achieved in the gentamicin group.*
9. • 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;34(8):1434–7. *This retrospective study is the only recent report comparing results of surgical intervention with intratympanic gentamicin for control of vertigo.*
10. • Lambert PR, Nguyen S, Maxwell KS, Tucci DL, Lustig LR, Fletcher M, et al. A randomized, double-blind, placebo-controlled

clinical study to assess safety and clinical activity of OTO-104 given as a single intratympanic injection in patients with unilateral Ménière's disease. Otol Neurotol. 2012;33(7):1257–65. *This is the only randomized, double-blind, placebo-controlled clinical study reviewed. In addition, the study introduces the use of a novel, longer-acting steroid preparation.*

11. Monsell E, Balkany T, Gates G. Committee on hearing and equilibrium guidelines for the diagnosis and evaluation of therapy in Menière's disease. Otolaryngol Head Neck Surg. 1995;113(3): 181–5.
12. Itoh A, Sakata E. Treatment of vestibular disorders. Acta Otolaryngol Suppl. 1991;481:617–23.
13. Hamid M, Trune D. Issues, indications, and controversies regarding intratympanic steroid perfusion. Curr Opin Otolaryngol Head Neck Surg. 2008;16(5):434–40.
14. Parnes LS, Sun AH, Freeman DJ. Corticosteroid pharmacokinetics in the inner ear fluids: an animal study followed by clinical application. Laryngoscope. 1999;109(7 Pt 2):1–17.
15. Trune DR, Kempton JB, Harrison AR, Wobig JL. Glucocorticoid impact on cochlear function and systemic side effects in autoimmune C3.MRL-Faslpr and normal C3H/HeJ mice. Hear Res. 2007;226(1–2):209–17.
16. Hu A, Parnes LS. Intratympanic steroids for inner ear disorders: a review. Audiol Neurootol. 2009;14(6):373–82.
17. Garduño-Anaya MA, Couthino De Toledo H, Hinojosa-González R, Pane-Pianese C, Ríos-Castañeda LC. Dexamethasone inner ear perfusion by intratympanic injection in unilateral Ménière's disease: a two-year prospective, placebo-controlled, double-blind, randomized trial. Otolaryngol Head Neck Surg. 2005;133(2): 285–94.
18. Sennaroglu L, Sennaroglu G, Gursel B, Dini FM. Intratympanic dexamethasone, intratympanic gentamicin, and endolymphatic sac surgery for intractable vertigo in Meniere's disease. Otolaryngol Head Neck Surg. 2001;125(5):537–43.
19. Phillips J, Westerberg B. Intratympanic steroids for Ménière's disease or syndrome. Cochrane Database Syst Rev. 2011;7: CD008514.
20. Schuknecht H. Ablation therapy in the management of Ménière's disease. Acta Otolaryngol Suppl. 1957;47(s132):1–42.
21. Lange G. Gentamicin and other ototoxic antibiotics for the transtympanic treatment of Meniere's disease. Arch Otorhinolaryngol. 1989;246(5):269–70.
22. Lyford-Pike S, Vogelheim C, Chu E, Della Santina CC, Carey JP. Gentamicin is primarily localized in vestibular type I hair cells after intratympanic administration. J Assoc Res Otolaryngol. 2007;8(4):497–508.
23. • Huon L, Fang T, Wang P. Outcomes of intratympanic gentamicin injection to treat Meniere's disease. Otol Neurotol. 2012;33(5):706–14. *This meta-analysis reviews vertigo control, tinnitus, aural fullness and hearing outcomes following intratympanic gentamicin therapy, with multiple dosing strategies included in the pooled data.*
24. Derebery MJ, Fisher LM, Berliner K, Chung J, Green K. Outcomes of endolymphatic shunt surgery for Ménière's disease: comparison with intratympanic gentamicin on vertigo control and hearing loss. Otol Neurotol. 2010;31(4):649–55.
25. • Casani AP, Piaggi P, Cerchiai N, Seccia V, Franceschini SS, Dallan I. Intratympanic treatment of intracts unilateral Meniere disease: gentamicin or dexamethasone? A randomized controlled trial. Otolaryngol Head Neck Surg. 2012;146(3):430–7. *This randomized controlled trial compares results of intratympanic gentamicin with dexamethasone. Significantly higher vertigo control rates were obtained in the gentamicin group.*
26. Chia SH, Gamst AC, Anderson JP, Harris JP. Intratympanic gentamicin therapy for Ménière's disease: a meta-analysis. Otol Neurotol. 2004;25(4):544–52.
27. Radtke A, Lempert T, Gresty MA, Brookes GB, Bronstein AM, Neuhauser H. Migraine and Meniere's disease: is there a link? Neurology. 2002;59(11):1700–4.
28. Silverstein H, Smouha E, Jones R. Natural history vs. surgery for Meniere's disease. Otolaryngol Head Neck Surg. 1989;100:6–16.
29. Nguyen KD, Minor LB, Della Santina CC, Carey JP. Time course of repeated intratympanic gentamicin for Ménière's disease. Laryngoscope. 2009;119(4):792–8.