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Intratympanic (IT) Therapies for Menière's Disease: Some Consensus Among the Confusion

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Abstract

Purpose of Review—Aminoglycosides and corticosteroids are commonly used to treat Menière's disease. Intratympanic (IT) administration of these medications allows high inner ear concentrations without significant adverse systemic effects. As a direct result, IT therapy has grown in popularity. Recent studies have compared patient outcomes between IT aminoglycosides and corticosteroids. This review summarizes these findings.

Recent Findings—Trials comparing IT corticosteroids to IT placebo or oral therapy have had conflicting results. Most recently, Lambert et al. investigated the effect of IT dexamethasone in a sustained-release formulation compared to placebo. Their findings demonstrated improvement in some secondary measures of vertigo with the sustained-release formulation.

IT gentamicin is known to be effective in controlling vertigo in Menière's disease. In a recent study from 2016, Patel et al compared IT gentamicin and IT methylprednisolone in a double-blind, randomized controlled trial and identified no significant differences between the two in vertigo control.

Summary—IT injections of aminoglycosides and corticosteroids can improve vertigo control. Hearing and vestibular loss however may result with IT aminoglycosides. Corticosteroids demonstrate limited hearing loss but may not have the same efficacy in controlling vertigo. Further investigation in the etiology of Menière's disease is needed to tailor the proposed treatment to suit the disease mechanism.

Keywords

Menière's disease; intratympanic; aminoglycosides; corticosteroids

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Introduction

Menière's disease is a clinical syndrome where patients experience symptoms resulting from recurrent episodes of vertigo, hearing loss and fluctuating aural fullness and tinnitus [1–3]. Prevalence estimates have varied with reports ranging from 3.5 to 513 affected individuals per 100,000 [4–6]. Patients with Menière's disease can experience impairments to overall quality of life [7] and disease-specific quality of life [8, 9].

Prosper Menière, for whom the disease is named, first reported in 1861 a syndrome of spinning vertigo that he attributed to hemorrhage within the membranous labyrinth. Despite these initial reports linking inner ear disorder to spinning vertigo, inner ear hemorrhage has not been identified as a common cause of the disease that bears his name. The pathophysiology of what we now call Menière's disease remains unknown. Endolymphatic hydrops, however is a closely associated finding on temporal bone histology [10] and increasingly on contrast-enhanced magnetic resonance imaging as well [11, 12]. Since the cause(s) of Menière's disease are unknown there are no ideal therapies [13]. Nevertheless, clinicians continue to offer a myriad of treatment options to patients with Menière's disease including restrictions on oral salt consumption, medical management with diuretics, steroids or betahistine and surgeries such as decompression of the endolymphatic sac [14••]. In a comprehensive review of the available literature, Torok reported study authors consistently identified improvements in 60-80% of patients regardless of the intervention used [15]. Few studies have observed the natural history of the disease but among placebo-controlled studies, authors have reported over a 50% reduction in attack frequency at 9 months [16] and improvements in Menière's disease symptoms more broadly at one year [17].

In some patients with medically-refractory recurrent vertigo, ablative therapies (which destroy labyrinthine function) can reduce the frequency of vertigo episodes but sacrifice or carry risk for injury to residual hearing and vestibular function in the treated ear. Intratympanic (IT) therapies for the treatment of Menière's have become increasingly popular among otologists. Previously, patients whose symptoms persisted despite medical therapies were offered ablative surgeries such as vestibular nerve section or surgical labyrinthectomy. Since their introduction [18], IT injections have been offered by otologists as a less invasive option which can spare the patient general anesthesia and potentially avoiding damage to the membranous labyrinth and cochlea. Aminoglycoside antibiotics, for instance, are chemicals well known to be vestibulotoxic to inner ear hair cells and can be administered without general anesthesia, as a transtympanic injected solution. Aminoglycosides, however, can also adversely affect hearing and are expected to cause vestibular impairment. For this reason, IT corticosteroids have gained popularity as a therapy which may be effective in reducing vertigo episode frequency, without permanently impairing inner ear function. Several recent reports have studied IT therapies including aminoglycosides such as streptomycin and gentamicin, and corticosteroids such as dexamethasone and methylprednisolone. This review will aim to synthesize the latest findings and provide clarity to the treating clinician where possible.

Intratympanic Therapies

Treatments involving the middle ear predate our current understanding of otologic anatomy and physiology. These first treatments likely occurred accidentally though the application of various medical concoctions into a draining ear (i.e., perforations) which penetrated the tympanic membrane accessing the middle ear. A comprehensive review of IT therapies by Lustig (2004) highlights several important advancements in our understanding of the middle ear space and the interventional opportunities its position plays between the external and inner ears [19]. Prior to the acceptance of administering medication through the tympanic membrane, surgically ablative approaches (i.e., labyrinthectomy or vestibular neurectomy) were commonly considered standard approaches for symptom control. Currently, these surgical approaches are typically reserved for refractory symptoms [14••, 20]. IT drug delivery, however, is not without some risk. Rauch et al described a 1.6-3.9% risk of persistent perforation after treatment of sudden sensorineural hearing loss with IT corticosteroids [21, 22]. Other risks include local discomfort, inflammation (observed in guinea pigs after treatment with a sustained-release dexamethasone formulation [23]), otitis media or externa, transient vertigo caused by a caloric effect from the instilled fluid and sensorineural hearing loss (from aminoglycosides). Today, treatment decisions are dependent on symptom severity and progression. Groups that have attempted to construct algorithms to streamline clinical decision making [14••, 20] have emphasized using IT therapies early in the treatment pathway for Menière's disease, after lifestyle and dietary modification.

Aminoglycosides—Aminoglycoside antibiotics have a well-documented history of cochleotoxic and vestibulotoxic effects [24]. Within the bony labyrinth, several studies have investigated the trafficking and localization of aminoglycosides, finding different patterns of localization dependent upon the dose, duration, and route of administration. IT injected aminoglycosides appear to gain access to the inner ear via oval window and round window uptake [25, 26] through either active diffusion or endocytosis [27, 28]. Salt et al. recently quantified diffusion of gentamicin through the oval (35%) versus the round window (57%) [26, 29]. Access to these structures and their permeability, however, is not certain and may lead to variable exposure of drug to the inner ear [30–32]. Similar mechanisms of cellular trafficking (active diffusion and endocytosis) have been proposed in the transport of aminoglycosides into cells of the inner ear [33].

While most cells of the inner ear demonstrate aminoglycoside penetration, several studies have identified preferential loss of the inner hair cells at the basal turn of the cochlea and vestibular type I hair cells [34–38]. Direct damage to the spiral ganglion has also been observed [39] and histologic studies in rhesus monkeys suggest relative sparing of the maculae [40]. The degree to which a drug is cochleotoxic or vestibulotoxic differs among aminoglycosides. Gentamicin and streptomycin, for instance, are reported to be more vestibulotoxic. This feature has been used by otologists to control the vestibular symptoms of Menière's disease, initially provided through systemic delivery by Fowler [41] and subsequently through IT injections by Schuknecht [42, 43]. Use of streptomycin has been largely replaced by gentamicin which is thought to be more selectively vestibulotoxic and better able to preserve residual hearing [44]. IT delivery of aminoglycosides is regularly

used by otologists in the control of the fluctuating vestibular symptoms associated with Menière's disease.

IT Streptomycin: Described for the first time in 1944 [45], streptomycin was quickly adopted for chemical ablation of inner ear function. Five years after its introduction, streptomycin was administered intramuscularly by Fowler and Hamberger et al for this purpose [41, 46]. In 1956, Schuknecht began reporting his experience with reported performing IT streptomycin injections. While 63% (5 of 8) of the Menière's patients reported improvement of their vertigo they also experienced profound sensorineural hearing loss [42, 43]. Use of IT streptomycin continued until Silverstein's 1979 review, which recommended abandoning streptomycin due to his experience in two patients with Menière's disease who had unpredictable responses and experiences with rapid hearing loss [47]. Similarly, Lange reported excellent control of vertigo (96%, 50 of 52 patients with complete vertigo control) but 24% experienced some degree of hearing loss post-treatment [48]. The rate of hearing loss prompted Lange's recommendation to administer gentamicin rather than streptomycin.

Occasional reports on the use of streptomycin for vertigo control have continued although gentamicin has become the preferred aminoglycoside for chemical ablation of vestibular function. Jung and colleagues evaluated the quality of life (QOL) via the Menière's Disease Outcomes Questionnaire-Retrospective Version (MDOQ-R) after powdered streptomycin was applied to the middle ear space in patients with Menière's disease [49–51]. In addition to improvements in QOL, IT streptomycin yielded nearly a 59% complete control of vertigo (AAO-HNS Class A (no vertigo)); however, this value is lower than rates of complete vertigo control reported by other studies in which IT gentamicin was used [52]. More recently, Kim et al reasserted the use of powdered streptomycin directly applied to the round window [53]. They reported vertigo control in 83% of patients with 18% (18 of 98 patients) experiencing a greater than 10 dB HL hearing loss and 4 patients who experienced a greater than 30 dB HL hearing loss.

IT Gentamicin: Gentamicin has become the most commonly used aminoglycoside for treatment of vestibular symptoms associated with Menière's disease. While gentamicin is believed to be less cochleotoxic than streptomycin, some patients still develop hearing loss [33, 43]. A review of this institution's experience (Johns Hopkins Hospital) revealed 17% of patients treated with IT gentamicin experienced decreased hearing which were similar to patients treated conservatively [54]. This risk may be minimized by limiting the dose administered. Beck and Schmidt found that limiting the number of doses and by stopping treatment at the first sign of inner ear damage, rates of hearing loss were decreased (hearing deterioration in 15% vs 58%) while vertigo symptoms (92.5% vs 95% with improved or resolved vertigo) and overall satisfaction with treatment (86% vs 95% satisfaction) were maintained [55]. Several groups subsequently reported their experiences with a variety of protocols altering dosing regimens, interval of treatment or by stopping at the onset of symptoms with varying degrees of success related to vertigo symptom control and hearing preservation [56–62]. Early protocols resulted in hearing loss rates ranging between 30-45% of patients receiving IT gentamicin but these rates have decreased in newer protocols. One

long term (>2 years from treatment) follow up study by Nedzelski reported vertigo control of AAO-HNS class A (i.e., no vertigo) in 84% of subjects and class B (i.e., vertigo attacks of 1%–40% of pretreatment rate) in 8% of subjects with 26% experiencing worsening hearing [63]. Clinicians soon realized that the ototoxic effects of IT gentamicin were delayed 2-3 days which eventually led clinicians to develop titration protocols using fewer and less frequent injections and close monitoring for ototoxicity [64–67]. While this approach resulted in less hearing loss, perhaps as expected, there was slightly worse vertigo symptom control as well.

To date, there have only been a few interventional randomized controlled trials investigating the role of IT gentamicin in the treatment of Menière's disease. In 2011, Pullens and van Benthem reviewed the literature for the Cochrane Collaboration and identified seven interventional studies relating to IT gentamicin and Menière's disease [68]. Only two of these studies were randomized controlled trials (RCT's) and met all of their inclusion criteria to be accepted in their analysis. Similarly, in 2015, Syed and colleagues published a systematic review investigating randomized controlled trials of IT therapies for Menière's disease focusing on the same two randomized controlled trials [69]. In the first trial, Stokroos and Kingma (2004) reported results from their prospective randomized double-blind placebo-controlled trials establishing the efficacy of IT gentamicin compared to placebo in patients with active unilateral Menière's disease [70]. Using the titration method, injections were performed every six weeks until symptoms were controlled. They found IT gentamicin decreased the number of vertiginous attacks per year from 74±114 pre-treatment to 0 post-treatment ($p = 0.002$) compared to placebo (25±31 and 11±10, $p = 0.028$) with no clinically significant change in hearing in either group at six months follow up. However, Pullens and van Benthem noted significant heterogeneity in the number of vertiginous attacks in the pretreatment period (74 ± 114 attacks in the interventional group and 25 ± 31 in the placebo group reported in the year prior to inclusion) [71]. In a follow-up retrospective study in 2007 by the same group, the authors reported complete vertigo control in only 61.4% of patients and partial control in 19.3% of patients with a titration schedule of at least 27 days between injections [72].

In the second second trial in the Cochrane review, Postema and colleagues (2008) similarly conducted a prospective, double-blinded, randomized, placebo-controlled trial in patients with unilateral Menière's disease [73]. The authors also selected the titration method. In this study a pressure equalization (PE) tube was placed 4 weeks prior to the start of therapy and 0.4 ml of 30 mg/ml gentamicin was administered weekly for 4 weeks. Data were collected on pure-tone audiometry and subjective evaluations of vertigo, aural fullness, and tinnitus rated on a 4-point scale: (3) severe, (2) moderate, (1) mild, and (0) none. There were decreases in both the aural fullness score (1.7 ± 1.0 [mean ± SD] before to 0.9 ± 1.1 after) and vertigo score (2.1 ± 0.8 before to 0.5 ± 0.6 after study) in the gentamicin group but no changes in the placebo group for aural fullness (1.8 ± 1.0 before to 1.8 ± 1.1 after treatment) or vertigo (2.0 ± 0.8 before versus 1.8 ± 1.0 after treatment). Hearing levels and tinnitus did not significantly change in either group at the 12 month follow-up visit. The Cochrane Collaboration concluded IT gentamicin can be an effective treatment for vertigo in Menière's disease with a potential risk of hearing loss. There were recommendations for low-dosage administration with longer intervals between treatments [68].

Others performed more inclusive systematic reviews and meta-analyses with the goal of using all available prior data to determine the safety and effectiveness of IT gentamicin. [69, 74–78•] In 2012, Houn et al. [77] published a comprehensive systematic review with meta-analysis. Reviewing available studies through 2011, the authors focused on studies investigating the use of IT gentamicin in randomized controlled trials (n = 2) and prospective cohort studies with greater than 10 subjects (n = 12). They reported 87.5% (confidence interval 81.5%-92.0%, $p < 0.001$) of patients achieved substantial vertigo control (AAO-HNS class A [71.4%] and class B [16.1%] vertigo control). When comparing fixed dose versus titration protocols, the authors reported successful symptom control in 87.5% (range, 56.3%-97.5%) of patients receiving fixed doses, and 88.2% (range, 71.0%-97.1%) of those who followed a titration protocol without significant differences between groups ($p = 0.94$). In their systematic review Cohen-Kerem et al. similarly found 90.7% substantial vertigo control (71.4% complete control) in their pooled meta-analysis and no differences between fixed dose and titration protocols [76]. Despite using similar source articles, Chia et al, however, found a significant difference between treatment approaches (fixed dosing versus titration) with titration protocols performing better at achieving complete vertigo control, 81.7% versus 66.7% [75].

Similar to the Houn et al. and Cohen-Kerem et al. reviews, Diamond and colleagues [74] also found no significant differences in vertigo symptom control between the two dosing approaches (fixed versus titration). The authors did note, however, a trend of increased hearing loss with more frequent dosing (e.g., 32% with dosing multiple times daily, 26% for daily dosing, and 21% for weekly dosing). Houn et al. and Cohen-Kerem et al. found hearing was not significantly affected by either treatment paradigm (weighted mean PTA 2.2 [± 2.0] dB and 4.1 [± 2.9] dB for fixed and titration protocols respectively, $p = 0.09$ [77]). Other findings from systematic reviews include better tinnitus control with the titration method ($p = 0.02$), equivocal improvements in aural fullness ($p = 0.06$) and overall improved QOL scores (n = 7 studies) [77]. From their review Houn et al. [77] suggested that while a minimal cumulative dose of 13.4 mg may be predictive of treatment success, additional studies to determine optimal dosage, however, are needed.

Most recently, Vlastarakos et al. [78•] published a systematic review looking at sustained-release delivery of IT gentamicin (dynamic-release versus sustained-release vehicles). Dynamic release (microcatheter at the round window) was found to provide satisfactory vertigo control in 89.3% (70.9% reporting complete control). Sustained-release preparations (gentamicin soaked wick/pledget) provided 82.2% satisfactory control in the pool patients (75% with complete control). In patients receiving sustained-release preparations, complete hearing loss was reported in 31.1% patients with another 23.3% of patients experiencing partial hearing loss. This adverse change in hearing was unacceptably high, reinforcing the suggestion of using a sustained-release vehicle only in patients who had failed IT gentamicin injections previously or those without serviceable hearing.

Corticosteroids—While the pathophysiology of Menière's disease is unknown some have theorized Menière's disease may be immune-mediated [79], thereby providing a rationale for the use of immunosuppressive corticosteroids as a treatment. Further support was provided by the observation that IT injection of dexamethasone reduced endolymphatic hydrops as

reflected by electrocochleography one month following treatment [80], a finding which was not sustained at one year follow-up [81]. This also suggested that patients with recurrent Menière's disease may require repeated treatments with IT steroids. Dexamethasone has also been shown to upregulate epithelial sodium transport suggesting it may not be acting directly as an anti-inflammatory [82]. In an autoimmune mouse model, it was concluded that the inner ear mineralocorticoid effects are more likely to be responsible in preserving hearing rather than the glucocorticoid effects [83]. The first trials of IT dexamethasone for Menière's disease were conducted by Itoh and Sakata in the 1980s [84] and IT steroids have slowly gained popularity as a less invasive treatment compared to surgery and as an alternative to IT gentamicin.

IT steroid options include dexamethasone and methylprednisolone. Studies in guinea pigs showed IT injected methylprednisolone had higher inner ear fluid concentrations for longer durations compared to dexamethasone [85] when corrected for anti-inflammatory potency. When comparing IT to intravenous (IV) corticosteroid administration in humans both IT methylprednisolone and dexamethasone reached perilymph concentrations more than 200 times higher compared to IV administration [86]. As high dose dexamethasone is not commonly available in many European countries, methylprednisolone (62.5mg/ml) injections are often used instead [87••]. It should be noted that methylprednisolone is not favored by some authors due to burning discomfort often associated with application to the middle ear.

IT Methylprednisolone: Two retrospective studies of patients who underwent IT methylprednisolone injections reported at least short-term control of vertigo with variable long-term effects [88], [89]. Gabra et al compared IT methylprednisolone to IT gentamicin retrospectively in 89 patients and showed better control of vertigo, tinnitus, and aural fullness with gentamicin [90].

In 2016, Patel and colleagues published a randomized, double-blind comparative effectiveness trial for 60 adults with refractory unilateral Menière's disease comparing 2 doses of IT 62.5 mg/ml methylprednisolone to IT 40 mg/ml gentamicin given 2 weeks apart [87••]. Their main outcome measure was vertigo frequency during months 18-24 after starting treatment compared to vertigo frequency during the 6 months prior to starting therapy. The authors reported equally effective vertigo control in each group. Specifically, there was an 87% reduction in vertigo frequency in the gentamicin group compared to a 90% reduction in the methylprednisolone groups with similar mild adverse events. Though there was no difference in hearing levels, the gentamicin group demonstrated a decrease in speech discrimination. As expected, the gentamicin group experienced unilateral vestibular loss while the methylprednisolone group had preserved vestibular function. The study concluded that both IT methylprednisolone and gentamicin represent safe and effective therapeutic options for those with refractory unilateral Menière's disease.

IT Dexamethasone: Silverstein et al carried out an early prospective, randomized, double-blind, placebo-controlled crossover study comparing IT 8 mg/ml dexamethasone with IT saline placebo in the 1990s [91]. A total of 20 patients received 1 intervention for 3 consecutive days and after 3 weeks switched to the other intervention for 3 consecutive days.

The aim was to determine the effect of IT steroids on hearing loss and tinnitus. The study found no significant difference in these outcomes. However, none of the patients had disabling vertigo and the frequency/severity of vertiginous episodes were not studied as outcome measures.

Garduno-Anaya et al. [92] conducted a prospective, randomized, double-blind, placebo-controlled study comparing IT 4 mg/ml dexamethasone injections administered over 5 consecutive days to IT saline placebo in 22 patients. This study showed statistically significant improvements in vertigo control, subjective hearing loss, tinnitus and aural fullness with IT dexamethasone. A Cochrane review in 2011 [93] noted this RCT as the only study to meet rigorous inclusion criteria but concluded there was limited evidence to support the effectiveness of IT steroids for the treatment of Menière's disease.

Since then, two systematic reviews of IT corticosteroid injections for Menière's disease have reviewed four other RCT's. Both reviews favored IT steroids as a treatment option [94]. Two trials additionally compared IT dexamethasone with gentamicin. One RCT comparing IT dexamethasone (4 mg/ml, 3 injections once every 3 days) with gentamicin showed a higher rate of vertigo control with gentamicin compared to dexamethasone without significant differences in hearing outcomes [95]. Another prospective, non-randomized study by Sennaroglu et al compared instillation of 5 drops of 1 mg/ml dexamethasone through a pressure equalizing (PE) tube every other day for 3 months with gentamicin [96]. While there was no difference in vertigo control between the two treatment groups, 13% of patients in the gentamicin arm suffered “total” hearing loss. Despite the potential increased rate of vertigo control with gentamicin, Lavigne et al. preferred dexamethasone to avoid the risk of cochleotoxicity with gentamicin [94].

Two other trials compared IT dexamethasone to medical therapy. Paragache et al compared application of 0.2 mg/ml dexamethasone to the middle ear through a ventilation tube for 3 months and demonstrated no difference in vertigo control, tinnitus or aural fullness compared to conventional medical therapy of dietary restriction and oral betahistine 16 mg 3 times daily [97]. Another study comparing IT high-dose 4 mg/ml dexamethasone every 3 days for 3 doses to high-dose 144 mg daily oral betahistine similarly showed no difference in vertigo and tinnitus control [98]. As a result, IT dexamethasone may be comparable to oral betahistine in treatment of Menière's with the benefit of achieving the same effect with a few quick procedures as opposed to a chronic daily medication. However, a recent multicenter, double blind, randomized, placebo-controlled, dose-defining trial from Germany showed no difference in vertigo attacks between oral betahistine at low dose (24 mg two times daily), high dose (48 mg three times daily), and placebo [16]. As such, oral betahistine and by extension, IT dexamethasone, may be working through a placebo effect.

Lack of consensus among studies regarding ideal dexamethasone administration frequency and dose may be responsible for the heterogeneity in outcomes. To determine the effect of administration frequency, one study compared daily versus weekly IT 4 mg/ml dexamethasone administration and showed no significant difference in vertigo control [99]. To determine the effect of dose, a multicenter, randomized, double-blinded, placebo-controlled trial compared a single IT injection of 12 mg and 3 mg dexamethasone in a time-

release gel to placebo and demonstrated reduced vertigo frequency with the 12 mg dose [100]. This trial also assessed the safety of a dexamethasone formulation in a glycol polymer which gels at body temperature, thereby allowing more sustained exposure of the inner ear to the steroid compared to an aqueous formulation. A Phase 2b multicenter study compared a single IT injection of 12 mg dexamethasone of this sustained-release formulation to placebo. There was no statistically significant difference between the groups in the change from baseline vertigo rate and at month 3 follow-up (placebo [-43%], OTO-104 [-61%], $p = 0.067$) [101•]. There were improvements, however, in the number of days with definitive vertigo and daily vertigo counts [101•]. A Phase 3 trial is currently ongoing. As such, the efficacy of dexamethasone may be an issue of appropriate dose and sufficient time of inner ear exposure to the drug.

Other IT Therapies

Other IT therapies used as therapy for Menière's disease include antiviral agents such as ganciclovir [102] as recurrence of a neurotropic virus has been suggested to be an etiology of Menière's disease. Even so, a prospective double-blind study showed no difference in outcomes. IT lidocaine for labyrinth anesthesia is another option with some retrospective studies suggesting efficacy [103]. However, no prospective, randomized controlled trial has been conducted. Latanoprost, commonly used to reduce intraocular pressure in glaucoma, may also act through the same receptors to decrease endolymphatic hydrops. It was studied in a small placebo-controlled, double-blind, crossover trial and showed improvement in vertigo and hearing compared to placebo [104]. Pinsetta et al described the synthesis of a neamine-derived pseudodisaccharide which caused vestibular damage but spared the cochlea in an animal model [105]. This compound may be superior to gentamicin to circumvent gentamicin's cochleotoxic effects but to date there have been no human trials.

Ongoing Clinical Trials

There are several prospective, double-blinded, randomized, placebo-controlled clinical trials underway. According to the U.S. National Institutes of Health Clinical Trials website (www.clinicaltrials.gov), several studies are focusing on IT injections for controlling vertigo frequency. As previously mentioned, a Phase 2 prospective, double-blinded, placebo-controlled clinical trial is evaluating the safety, efficacy and duration of action of IT latanoprost. According to phase 1 results, latanoprost significantly reduced vertigo in 30% of patients and improved speech discrimination scores in 15% of their participants compared to placebo. Those who received placebo, however, had a decrease in the intensity of their tinnitus whereas the latanoprost cohort did not [104]. Another ongoing trial is a multicenter, prospective, randomized, double-blind, placebo-controlled, Phase 3 study of OTO-104 given as a single IT injection. There are several other clinical trials involving orally administered interventions, however, due to the scope of this article, their results have not been reported (Table 1).

Conclusions

A clinical diagnosis of Menière's disease is made with a patient history characterized by recurrent episodes of vertigo lasting 20 minutes or longer, typically accompanied by a low-

frequency sensorineural hearing loss and fluctuating aural fullness and tinnitus. Most therapies are targeted at alleviating the symptoms of vertigo. For those who do not experience improvement of their symptoms with conservative medical management (e.g., low salt diet, diuretics, betahistine), intratympanic injections of corticosteroids and aminoglycosides have been proven to provide benefit in reduction of vertigo frequency and other symptoms of Menière's disease. When dosed conservatively and using a titration schedule with infrequent dosing, IT gentamicin provides good control of vertiginous symptoms with minimal risk to hearing [69, 74–77]. Hearing loss and vestibular hypofunction, however, continue to be a risk of IT gentamicin due to its ablative nature and cocheotoxicity [69, 74–78•]. Vestibular hypofunction is often associated with imbalance during rapid ipsilateral head movements and other symptoms such as oscillopsia [106, 107].

Studies are often hindered by the natural course of the disease, however, in which vertiginous symptoms tend to improve and hearing loss progressively worsens over time. Symptoms become less severe and disappear after 2-8 years in 60% to 80% of those suffering from the disease [108]. Patients often demonstrate variability in the severity of their symptoms and the degree of the end organ damage. Clinical trials which do not consider time to be a valid therapy and do not have a placebo arm to their study should be considered flawed [14••]. In addition, studies which do not recognize the tendency of patients to seek therapy when their symptoms are at their most severe, create the illusion of therapeutic efficacy due to the intervention, all while ignoring the patient's symptomatic regression to his/her mean.

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Table 1

List of current clinical trials registered as recruiting on the ClinicalTrials.gov and NHS sites in 2017.

Study	Principal Investigator	Sites	Phase	Status	Study Design	Population	Drug	Intervention Method
A Prospective, Randomized, Double-blind, Placebo-controlled, Multicenter, Phase 3 Study of OTO-104 Given as a Single Intratympanic Injection in Subjects With Unilateral Menière's Disease	Carl LeBel, Ph.D.	Multiple sites in USA, and Europe	Phase 3	Recruiting	Randomized	Adults with Unilateral Menière's disease by 1995 AAO-HNS criteria	OTO-104 (dexamethasone sustained-release formulation) vs Placebo	IT Injection
Lamotrigine for Menière's Disease: a Double-blind, Placebo-controlled Pilot Study	Lixin Zhang, M.D., Ph.D.	Dent Neuroscience Research Center, Amherst NY	Phase 3	Recruiting	Randomized	Adults with Unilateral Menière's disease by 1995 AAO-HNS criteria	Lamotrigine vs Placebo	Oral
Reduction of Plasma Vasopressin Level in Patients With Menière's Disease	Tadashi Kitahara, M.D., Ph.D.	Osaka University, Suita-city, Osaka, Japan	N/A	Recruiting	Randomized	Patients diagnosed as Menière's patients according to the 1995 AAO-HNS criteria	None	Lifestyle
Phase 1b Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics of SPI-1005 in Menière's Disease	Jonathan Kil, M.D.	Multiple sites in USA (CA, NY, SC, WA)	Phase 1	Invitation	Randomized	By invitation, Adults with Unilateral Menière's disease by 1995 AAO-HNS criteria	SPI-1005 (small molecule mimics glutathione peroxidase) vs Placebo	Oral

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