Otoprotectants: From Research to Clinical Application

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ABSTRACT

There is an urgent need for otoprotective drug agents. Prevention of noise-induced hearing loss continues to be a major challenge for military personnel and workers in a variety of industries despite the requirements that at-risk individuals use hearing protection devices such as ear plugs or ear muffs. Drug-induced hearing loss is also a major quality-of-life issue with many patients experiencing clinically significant hearing loss as a side effect of treatment with life-saving drug agents such as cisplatin and aminoglycoside antibiotics. There are no pharmaceutical agents approved by the United States Food and Drug Administration for the purpose of protecting the inner ear against damage, and preventing associated hearing loss (otoprotection). However, a variety of preclinical studies have suggested promise, with some supporting data from clinical trials now being available as well. Additional research within this promising area is urgently needed.

KEYWORDS: otoprotection, ototoxicity, noise-induced hearing loss, drug-induced hearing loss

THE NEED FOR OTOPROTECTIVE DRUG AGENTS

Adult hearing loss is commonly associated with age and noise exposure. The prevalence of hearing loss also varies with demographic factors such as sex, race/ethnicity, socioeconomic status, and educational level.[1,2]

Noise-induced hearing loss (NIHL) is typically identified as one of the most preventable forms of hearing loss, as hearing protection devices (HPDs, including ear plugs and earmuffs) can be worn when neither the sound level nor the exposure time can be decreased within safe limits. Nonetheless, NIHL is highly prevalent across the adult population, with analysis of the 2011–2012 National Health and Nutrition Examination Survey (NHANES) data suggesting that almost a quarter of the adult population has an audiometric notch consistent with and potentially indicative of NIHL.[3] Among adults reporting occupational noise exposure, the rate at which notched audiometric audiograms were

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detected increased to a third of the noise-exposed population.[3]

Better hearing loss prevention strategies that improve success with prevention of NIHL are urgently needed for military personnel as well, with the Veterans Administration (VA) reporting that noise-induced tinnitus and NIHL are the top two disabilities for which veterans of the armed services receive financial compensation.[4] There have been major efforts within industry to develop new HPDs and, compared with foam HPDs, assessment of these devices reveals significant improvements in sound quality with high fidelity HPDs[5,6] and significant improvements in detection and communication ability with electronic HPDs.[7–9]

Children are, of course, exposed to intense sound as well, although their exposure is more likely to occur during nonoccupational activities and exposure is likely to occur for shorter durations (<8 hours) and at less frequent intervals (<5 day/week) relative to workplace noise. Nonetheless, reports such as that of the World Health Organization[10] have driven tremendous interest in the prevention of NIHL in adolescents and young adults (for a recent discussion, see Le Prell et al).[11]

A second major cause of acquired hearing loss in children and adults is treatment with lifesaving pharmaceutical agents that are toxic to the inner ear (for a review, see Campbell and Le Prell).[12]

Drug-induced hearing loss (DIHL) often occurs as a side effect of treatment with lifesaving drug agents such as cisplatin and aminoglycoside antibiotics. Many of the agents that have been assessed for the prevention of NIHL also have assessed for potential prevention of DIHL, as there is significant overlap in the mechanisms of cell death that are activated by noise exposure and by ototoxic drugs. Although there is significant interest in drugs that will protect the inner ear and prevent hearing loss (otoprotective agents), there are currently no pharmaceutical agents approved by the U.S. Food and Drug Administration (FDA) for the purpose of hearing loss prevention, for either NIHL or DIHL.

The purpose of this review is to briefly discuss the agents that are currently registered in the National Library of Medicine's (NLM) Clinical Trials database (www.clinicaltrials.gov) as identified using search terms "noise induced hearing loss" and "temporary threshold shift."

Table 1 identifies clinical trials currently registered in the NLM Clinical Trials database (www.clinicaltrials.gov) as of October 5, 2018, using search terms "noise induced hearing loss" and "temporary threshold shift."

Drugs that are being assessed for prevention of DIHL were recently reviewed by Hammill and Campbell[13] and their systematic search was not replicated here. The NLM's clinicaltrials.gov Web site contains a clinical trial registry that allows doctors, patients, the public, and the research community to access information about current and completed clinical trials. By requiring that results be posted as part of the registry, it is also intended to reduce bias associated with the failure to publish negative results when a drug is not effective.

The FDA requires that applicable clinical trials (ACTs) be registered at clincialtrials.gov to be in compliance with Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801); when applications or submissions are made to the FDA, certification of compliance must be provided. In addition, the National Institutes of Health (NIH) requires that NIH-funded ACTs be registered (42 CFR Part 11).

Registration requirement rules were initially put into place for trials initiated after September 27, 2007; trials that were initiated before this date were required to be registered if they were ongoing as of December 26, 2007. The updated regulations described earlier in this paragraph became effective in January 18, 2017, and compliance was required as of April 18, 2017.

Many medical journals have now adopted policies that require registration of the clinical trial as a precondition for publication (http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html).

For the agents identified on clinicaltrials.gov, a brief summary of the published preclinical research and associated results from completed clinical trials is presented. Agents with clinical trial results posted are listed in Table 1 and discussed, followed by discussion of agents with

Table 1 Clinical Trials Currently Registered in the NLM's Clinical Trials Database (www.clinicaltrials.gov)

Study ID	Study title	Intervention	Sponsor	Status
NCT01444846	Otoprotection with SPI-1005 for prevention of temporary auditory threshold shift	Ebselen	SPI-1005, Sound Pharmaceuticals Inc	Completed, has results
NCT00808470	Micronutrients to prevent noise-induced hearing loss	β-Carotene, vitamins C and E, magnesium	University of Michigan	Completed, has results
NCT00552786	Antioxidation medication for noise-induced hearing loss	N-acetylcysteine (NAC)	National Taiwan University Hospital	Completed, has results
NCT02259595	Study to determine the safety, tolerability, and pharmacokinetic profile of HPN-07 and HPN-07 plus NAC	HPN-07 and NAC	Otologic Pharmaceutics, Inc.	Completed
NCT02257983	Protective effects of EPI-743 on noise-induced hearing loss	Vincerinone EPI-743	Edison Pharmaceuticals, Inc.	Completed
NCT00802425	Efficacy of AM-111 in patients with acute sensorineural hearing loss	AM-111	Auris Medical AG	Completed
NCT02903355	Phase 3 clinical trial: D-methionine to reduce noise-induced hearing loss (NIHL)	D-methionine	Southern Illinois University	Terminated
NCT02049073	Prevention of noise-induced hearing loss	Zonisamide and methylprednisolone	Washington University School of Medicine	Withdrawn
NCT01727492	Prevention of noise-induced damage by use of antioxidants	NAC and magnesium	University Hospital, Antwerp	Unknown
NCT02779192	A phase 2b study of SPI-1005 to prevent acute noise induced hearing loss (PANIHL)	Ebselen	SPI-1005, Sound Pharmaceuticals, Inc	Not yet recruiting

Note: Clinical Trials Currently Registered in the NLM's Clinical Trials Database (www.clinicaltrials.gov) as of October 5, 2018, as identified using search terms "noise induced hearing less" and "temporary threshold shift"
Abbreviation: NLM, National Library of Medicine.

completed studies but no posted results, and then other agents. It is beyond the scope of this review to discuss all agents ever tested in animal models or in humans for prevention of NIHL. For a comprehensive review across drugs assessed for the prevention of NIHL, readers should see the recent systematic review completed by Hammill[14]; additional detailed information can be found in the reviews by Le Prell and Bao[15] (animal studies) and Le Prell and Lobarinas[16] (human trials). For a more complete review and discussion of additional drugs that have entered clinical trials for prevention of DIHL, readers should see the recent reviews by Hammill and Campbell[13] and Le Prell et al.[17] Many of the drugs that are being assessed in human models are antioxidant agents that neutralize free radical formation in the outer hair cells and the lateral

wall, although other drugs of interest have different mechanisms of action.

Ebselen

One of the known mechanisms of action through which ebselen reduces or prevents NIHL is via the reduction of oxidative stress in the inner ear.[18] Ebselen reduces oxidative stress via action as a synthetic glutathione peroxidase (GPx) mimic and inducer in the ear,[19] and inhibition of enzymes that promote lipid peroxidation.[20] In culture, ebselen directly reduces cisplatin-induced reactive oxygen species (ROS) and reactive nitrogen species (RNS) formation, and cisplatin-induced lipid peroxidation, thereby increasing cell survival.[21] A more detailed review of the biochemical mechanisms of action is available in the review by Le Prell et al.[17] With respect to prevention of NIHL in rodent models, ebselen has reduced both permanent threshold shift (PTS)[19,20,22,23] and temporary threshold shift (TTS).[24] Relatively lower doses have been more effective than relatively higher doses, with oral administration being highly effective.[20,23] In other preclinical investigations assessing the potential to reduce or prevent DIHL, ebselen has attenuated cisplatin insult when used as a single agent[25] as well as when delivered in combination with allopurinol.[26,27] However, a study by Lorito et al[28] failed to detect protection from cisplatin ototoxicity.

Prevention of TTS in humans was demonstrated in NCT01444846, with dose-dependent benefits[29] (see Table 1 and "Disclosure" section). NCT02779192 is a second clinical trial including participants from multiple study sites which is currently listed on clinicaltrials.gov as not yet recruiting (see Table 1). A complete discussion of the drug development pathway for ebselen can be found in the review by Lynch et al.[30] Taken together, the preliminary data are promising, and additional research will be important in determining not only the repeatability and reliability of the observed protection against TTS in humans but also the specific patient populations who have the potential to benefit. Whether the current observations of protection against the moderate TTS induced in this clinical trial paradigm (i.e., ranging from 0 to ~20 dB TTS 15 minutes postexposure, with largely complete recovery typically observed within 3 hours[29,31,32]) will extend to protection against larger acoustic traumas remains to be determined, and PTS is also a question of interest for future studies. These latter studies are a challenge for all agents of interest, as these studies are much more difficult to design and complete for a variety of reasons (outlined in the "Research Needs" section).

β-Carotene, Vitamins C and E, and Magnesium

The combination of β-carotene, vitamins C and E, and magnesium (ACEMg)[33,34] was identified as a potential therapy of interest by Le Prell et al,[35] who suggested that combining multiple antioxidant agents in one formulation might allow each agent to be delivered at relatively lower doses. If so, this might improve the safety profile, while simultaneously improving overall therapeutic benefit if each of the antioxidants had different mechanisms of action.[35] Specific mechanisms of action for each of these active agents have been reviewed in detail previously.[15,17] In brief, each of these agents have antioxidant effects, although they differ with respect to solubility and the free radicals they have the greatest affinity for.

Pre-noise treatment with ACEMg reduced the effects of noise in guinea pigs and mice[35–37]; similarly, retinoic acid in combination with vitamins C and E and magnesium reduced PTS in mice.[38] Another compound with an increased number of active agents similarly reduced NIHL in rats (Acuval 400 multivitamin supplement: vitamins A, E, B1, B2, B6, and B12; L-arginine; ginkgo biloba; magnesium; selenium; zinc; and coenzyme Q10).[39] There has much less systematic investigation of ACEMg for the prevention of DIHL, although significant reductions in gentamicin-induced threshold shift and hair cell death were revealed when guinea pigs were treated with ACEMg in parallel to gentamicin.[40] We have also presented preliminary data suggesting similar protection against amikacin-induced hearing loss.[41] Single-agent applications have been much more commonly assessed for prevention of DIHL using micronutrient interventions; there have been mixed results across several diverse studies

and those data are reviewed in detail in the review by Le Prell et al.[17]

With respect to human clinical testing, the ACEMg combination has been assessed in human participants in two prospective randomized, placebo-controlled, double-blind, clinical trials, one of which is listed in Table 1 (NCT00808470, see "Disclosure" section). In NCT00808470, an experimental tablet-based dosing paradigm did not reduce or prevent TTS or noise-induced tinnitus.[32] In the other, earlier study completed in a partnership with members of the Karolinska Institute (see "Disclosure" section), potential prevention of TTS in soldiers completing weapons training was assessed, but no reliable TTS occurred in either the placebo or treatment group, which consumed an experimental capsule-based treatment.[42] Several studies have assessed potential prevention of DIHL in human patients, with little or no evidence of benefit in most studies.[43–45] Given these negative results, it is intriguing that several epidemiological analyses nonetheless suggest that healthier nutrient intake is generally associated with better hearing outcomes; however, these data rely on observed correlations and may or may not reflect any underlying causal relationships.[46–49] Even if dietary nutrients metabolized from fruits and vegetables are ultimately shown to confer improved hearing outcomes, there is not adequate evidence to conclude that specific nutritional supplements will provide parallel benefits, and we do not know what doses would be both safe and effective.

N-Acetylcysteine

N-acetylcysteine (NAC) has several mechanisms of action.[50,51] In brief, it is a cysteine prodrug and a GSH precursor, it can be oxidized by circulating free radicals or serve as an electron donor, and it can also bind with metal ions.[52,53] NAC has reduced PTS in studies using a variety of experimental designs, including both pre-noise prevention and post-noise rescue strategies (for reviews, see Le Prell and Bao[15] and Kopke et al[54]). In general, delaying treatment until after the noise exposure has ended has been less effective than beginning treatments prior to the noise insult; in addition, higher doses have generally been more effective than lower doses, with injections of NAC being more effective than treatments delivered orally (for detailed review, see Le Prell and Bao.[15]) Preclinical studies assessing prevention of cisplatin-induced hearing loss suggest the potential for drug–drug interactions between NAC and cisplatin; this has led to studies in which transtympanic[55,56] or delayed[57,58] NAC administration has been successfully used. NAC also has been shown to prevent gentamicin-induced ototoxicity in rats.[59]

Failure to reduce or prevent TTS in early human TTS-prevention trials led to escalating NAC doses in later TTS trials, with more success in studies using higher doses.[60–62] In the most recent investigation, positive outcomes were observed within a subset of the secondary analyses in U.S. Marine recruits exposed to impulse noise.[63] None of these studies were registered with clinicaltrials.gov, and they are not listed in Table 1. The single NAC study listed in Table 1, NCT00552786, was run out of the National Taiwan University Hospital and did not provide clear evidence of benefit based on the small TTS changes observed within both the NAC and placebo groups.[64] In this study, TTS was measured at the end of the workday in employees randomized into treatment and placebo conditions. Small changes in both NAC and placebo groups have been a challenge in at least one other study.[65]

NCT02259595, listed in Table 1, is a safety study for a novel drug agent (a combination of NAC and 4-OHBPN). Although prevention of NIHL is not being evaluated in this trial, NIHL is included as a keyword for that Phase 1 study, and this study was therefore included in Table 1 for completeness. NCT01727492 also proposes assessment of a NAC combination, with NAC and magnesium serving as active agents. Although the current status of the trial is unknown (see Table 1), a published protocol is available.[66] This protocol describes the recruitment of young adults attending loud recreational events.

In patients treated with cisplatin, prevention of hearing loss at high frequencies (i.e., 8 kHz and above) has been detected in several studies using either intratympanic[55] or oral[67] treatment, although other studies failed to

detect prevention of cisplatin-induced hearing loss using NAC.[56] Prevention of aminoglycoside-induced ototoxicity in patients enrolled in clinical trials has been relatively more mixed. Some data suggest early benefits that are not maintained at more extended time points,[68,69] whereas another study revealed no differences at early times, with significant differences emerging later in the follow-up period.[70] Despite mixed outcomes across test times, a systematic review and meta-analysis revealed reliable decreases in the relative risk of aminoglycoside-induced ototoxicity in NAC-treated patient participants (relative risk = 0.14, 95% confidence interval: 0.05–0.45).[71,72] NAC is currently used in cases of acetaminophen overdose, and interest in this agent, alone or in combination with other agents, is certain to continue. Further research is needed to determine optimal NAC dosing and route of administration to protect against ototoxicity related to noise, cisplatin, and aminoglycoside antibiotics.

Vincerinone and Coenzyme Q10

Vincerinone has a unique trajectory in that it was taken straight to the NCT02257983 clinical trial listed in Table 1 even though there were no published data documenting prevention of NIHL in an animal model (see "Disclosure" section). Although there were no published data documenting hearing loss prevention in animal models, this drug had shown positive outcomes in other mitochondrial disease models including Friedrich's ataxia,[73] Leigh's syndrome,[74–76] and other mitochondrial diseases.[77] With respect to chemical structure, EPI-743 shares some similarities with coenzyme Q10 and idebenone, although it was synthesized with important structural changes to improve bioavailability and potency.[77,78] Coenzyme Q10 has been well studied with respect to prevention of NIHL in animal models,[79–83] with more limited preclinical testing for prevention of cisplatin-induced hearing loss[84] and gentamicin-induced hearing loss.[84] Across studies, administration of Co-Enzyme Q10 has reduced cochlear trauma and hearing loss, including studies in which it is delivered in a water-soluble form (Q-Ter).

Preliminary human testing with Q-Ter, the water-soluble form of Coenzyme Q10, has been completed using a laboratory-based noise exposure, with participants having a significantly smaller TTS during treatment, relative to an initial untreated control exposure, as well as more rapid recovery of the TTS.[85] In addition, a pilot study in humans undergoing medically necessary cisplatin chemotherapy revealed improved hearing outcomes at 8 kHz, and a reduced rate of tinnitus, in patients receiving concomitant therapy with Acuval Audio which includes Q-Ter; vitamins B1, B2, B6, B12, and E; choline; melatonin; Ginkgo biloba extract; and Lactium milk protein hydrolysate.[86] Treatment of mitochondrial disease has been challenging in other disease conditions,[87] and results from the otoprotection trial posted on clinicaltrial.gov are not yet available.

AM-111

AM-111 is a proprietary formulation of D-JNK-1; D-JNK-1 is a cell-permeable peptide that reduces noise-induced apoptosis by inhibiting the phosphorylation of the transcription factor *c-Jun*.[88,89] During phosphorylation, a phosphorous group is added to a protein by kinase enzymes, with the phosphorous typically coming from adenosine-triphosphate (ATP)—biochemical cellular energy that is generated in the mitochondria. Prevention of this phosphorylation prevents protein degradation and other structural changes that alter the protein. Under conditions of stress such as noise, JNK moves from the cytoplasm into either the cell nucleus, where it induces expression of various transcription factors that can promote cell survival or cell death, or it can translocate to the cell mitochondria, where it activates biochemical events that activate caspases leading to cell death. The specific pattern of translocation and transcription factor upregulation depends on the specific noise trauma.[90,91]

AM-111 has been effective in reducing NIHL in animal models even with delayed treatment, and it has been most effective when delivered directly to the round window at least at the doses tested to date.[92,93] AM-111 has also prevented hearing loss associated with neomycin injection.[94] The human clinical trial listed in

Table 1, NCT00802425, was an open-label study using a gel formulation injected through the tympanic membrane in 11 patients who visited the emergency room reporting acoustic trauma related to firecrackers set off on New Year's Eve; recovery was observed, but no control group was included and it is not clear how much recovery might have been expected in the absence of the AM-111 intervention.[95] The challenges of intratympanic therapy were recently discussed by Lynch et al.[30] In brief, the most common adverse events are blood crusts on the tympanic membrane, which typically resolve with time.

D-Methionine

Methionine is an amino acid used as a building block for protein; it thus plays an important role in many biological functions.[96,97] One of the functions of methionine is promotion of the resynthesis of glutathione (GSH) in response to GSH depletion,[98] and it acts as an antioxidant.[98,99] Two stable forms of methionine are D-methionine (D-met) and L-methionine (L-met). Several reviews of the use of D-met are available.[100,101] In brief, D-met has effectively prevented PTS with either pre-noise[102] or post-noise[100,103] treatment onset. Moreover, D-met has effectively reduced NIHL even when administered at low doses.[104] Data in TTS models have had mixed results with only a subset of studies showing protection.[102,105–107] D-met was initially assessed for cisplatin otoprotection, and has been highly effective in those models regardless of the method of delivery.[108–112] It also has been effective in reducing ototoxicity associated with several different aminoglycoside antibiotics, including amikacin,[100] kanamycin,[113] and tobramycin.[114]

L-met has been less well investigated, but protection against cisplatin ototoxicity has been reported in rat models.[115,116] In the study by Reser et al,[116] both L-met and D-met compromised the antineoplastic activity of cisplatin in a breast cancer model in rats, when the otoprotective agents were delivered systemically. Interference with cisplatin also was shown for systemic L-met in the follow-up report by Li et al,[115] but with no antitumor interference detected when local application to the round window was used instead. Those results contrast with that of Cloven et al,[117] who did not detect significant compromises in antitumor activity in a rat model of ovarian cancer, using D-met as an otoprotective agent.

The clinical trial assessing D-met for prevention of NIHL, NCT02903355, was terminated (see Table 1). Per the final report to the Department of Defense, fewer than half of the subjects required by the power analysis were completed, and a much lower than expected incidence of hearing loss than originally projected further reduced study power.[118] Based on the promising reduction of cisplatin-induced hearing loss in animal models, a clinical trial assessing potential prevention of cisplatin-induced hearing loss also was conducted, and preliminary presentation of the results by Campbell et al[119] included report of reductions in high-frequency threshold shift. Minor gastrointestinal disturbances were reported in both the final report on NIHL prevention[118] and in publications describing use of a proprietary D-met formulation (MRX-1024, developed by Molecular Therapeutics Inc.) in healthy controls and patients with radiation-induced oral mucositis.[120,121] Taken together, the data from animal models have been highly compelling but as noted earlier for other agents of interest, additional data are needed to understand potential benefits in humans and the expected rate and severity of side effects.

Zonisamide and Methylprednisolone

The deregulation of calcium homeostasis has been implicated in noise injury. As per the detailed review by Le Prell and Bao,[15] there are at least five types of Ca^{2+} channels (L-, N-, P/Q-, R-, and T-type). Although they have different pharmacological profiles, they have been broadly classified into low- and high-voltage activated channels, with the L-type and T-type channels perhaps being the best characterized channels.[122–124] Several L-type Ca^{2+} channel blockers, including diltiazem, nimodipine, verapamil, and nicardipine, have been shown to dose dependently reduce both OHC loss and PTS induced by noise.[125] Other studies have focused on T-type Ca^{2+} blockers, and both ethosuximide and trimethadione

significantly reduced noise-induced PTS and increased OHC survival in the hook region of the mouse cochlea.[126] Bao et al[127] assessed ethosuximide and zonisamide (which block T-type Ca^{2+} channels) and dexamethasone and methylprednisolone (synthetic glucocorticoid steroids) in mice for prevention of PTS and identified synergistic benefits associated with two-drug combinations, with zonisamide plus methylprednisolone identified as particularly effective. The combination of zonisamide plus methylprednisolone is being pursued for clinical testing at Washington University (NCT02049073), although this trial is currently identified as withdrawn.

Research Needs

Currently, there are few identified clinical trial populations in which the prevention of NIHL can be readily investigated. A few clinical trials have enrolled service members required to use firearms as part of their military training.[42,63,65,118] Across studies, NIHL was smaller than expected, reducing study power and in some cases precluding insight into potential benefits of the otoprotective agent used in the study. Workplace interventions also have been attempted,[64] with NIHL again being smaller than expected, limiting insight into the potential for otoprotection. In these kinds of field studies, smaller-than-expected changes in hearing may be a consequence of the improved use of HPDs while participating in the clinical trial. However, even in controlled laboratory studies during which a calibrated sound exposure is delivered directly, clinical trial participants have on average had smaller changes in hearing[29,32] than participants in preliminary studies tested as part of the development of the clinical trial methodology.[31]

Another approach that is less likely to be confounded by variable HPD use, but which perhaps has increased real-world relevance, is the recruitment of participants who attended real-world music events where HPD use is not mandatory.[61,66] Although HPD use at concerts or other amplified music events is effective in reducing TTS associated with such events,[128,129] many concert goers choose not to use HPDs at music events, an observation that also has generated significant interest in factors that influence decisions on HPD use.[130–132] Unfortunately, sound levels are variable across recreational settings,[133] and even if all participants were to attend music events at the same venue, collection of data across multiple nights can still result in significant variability in exposure level across participants.[61] An additional challenge to studies of recreational sound-induced TTS is the rapid recovery of TTS after such events, although changes on speech-in-noise tests appear to recover more slowly, perhaps extending the observation window for follow-up testing into the day after the event.[133]

Selection of primary and secondary outcomes must be carefully considered. Although Kopke et al[63] had some success in measuring otoprotection in their secondary analyses, PTS meeting the significant ototoxic change criteria (the primary outcome) of the American Speech Language Hearing Association (ASHA) was less prevalent than expected. This is perhaps not surprising however, as ASHA's significant change criteria include $\geq$20 dB threshold shift at any one frequency, $\geq$10 dB shift at any two adjacent frequencies, or loss of response at any three adjacent frequencies, with replication of the change required.[134] Although these ototoxic change criteria appear to be both sensitive and specific for DIHL (with few false positives), the typical pattern of noise injury in the above clinical trial populations is unlikely to drive changes of that magnitude except in cases of acoustic trauma. PTS studies are therefore a challenge across agents of interest, not only because PTS has been smaller than expected in early studies[63,118] but also because these studies are simply much more difficult to design and complete. Occupational NIHL is slowly progressive, accumulating over many years; study durations may require several years of monitoring in some populations. When study durations increase, participant attrition is expected to increase, as participants may change jobs, move, or otherwise become unwilling or unable to continue their participant. Variable use of HPDs not just across participants but also within individual participants on a day-to-day basis will introduce variability into the rate of progression of any NIHL. All of the above will

drive a need for increased sample sizes to compensate for the decreased study power that accompanies all of the above. Last but not least, there are important ethical considerations regarding additional HPD interventions for participants observed to have small year-to-year decreases in their hearing. Changes in hearing measured during the required annual tests should be communicated to workers, with retraining and/or refitting of HPDs, in an effort to prevent loss. Retraining should be included in the study protocol, to assure participants are not placed at increased risk for NIHL as a consequence of study participation.

SUMMARY AND CONCLUSIONS

Exciting progress has been made in recent years, with several new companies attempting to move forward with clinical development and testing of novel drug agents. Progress has been made with several completed trials both for NIHL and DIHL. Although there is not yet good consensus around clinical test paradigms and primary outcomes, active discussions and efforts to derive consensus are underway.[135–137] NIHL and DIHL are clinically significant issues, and given the number of agents of interest with positive preclinical supporting data, there is good reason to hope that one or more otoprotective agents will ultimately be effective in clinical testing and approved by the FDA. Because some of the active agents discussed in this review can be purchased over the counter (OTC) as dietary supplements (i.e., β-carotene, vitamins C and E, magnesium, NAC, coenzyme Q10, L-met), some patients may question whether they should take dietary supplements. Such patients should be informed regarding the lack of data directly establishing benefit, and lack of information regarding doses that might have benefit. For overall health purposes, the U.S. Institute of Medicine publishes both recommended daily intake values and upper daily limits for vitamins and minerals for healthy adults and children.[138–141] Those tables can be consulted for potential intake recommendations; however, it must be remembered that there are different contraindications for different OTC agents in individuals with various health issues. Moreover, information on herbal supplements is less systematic with respect to safety data and recommendations for use. One comprehensive source of information is MedlinePlus (https://medlineplus.gov/druginfo/herb_All.html). It is in the patient's best interest to speak with their physician about any dietary supplements, and patients should be counseled accordingly.

DISCLOSURE

Funding for previously completed clinical trials evaluating prevention of temporary threshold shift in humans was provided by U01 DC 008423 from the National Institutes of Health – National Institute on Deafness and other Communication Disorders (NIH-NIDCD). Clinical trial material used in that study included a tablet formulation of ACEMg developed by OtoMedicine, Inc. and a capsule formulation of ACEMg developed by Hearing Health Sciences, Inc. Specifically, NCT00808470 was a clinical trial completed at the University of Florida under the oversight of C. Le Prell with funding from the National Institutes of Health using clinical trial material provided by Hearing Health Science, Inc., and the study completed by the Karolinska Institute team was coordinated out of the University of Florida by C. Le Prell with funding from the National Institutes of Health and using clinical trial material provided by OtoMedicine, Inc. Additional funding and clinical trial material were provided via contracts to the University of Florida by Sound Pharmaceuticals, Inc. (Ebselen, SPI-105) and Edison Pharmaceuticals, Inc. (Vincerinone, EPI-743). Specifically, NCT01444846 was a clinical trial completed at the University of Florida under the oversight of C. Le Prell with funding and clinical trial material provided by Sound Pharmaceuticals Inc. and NCT02257983 was a clinical trial completed at the University of Florida under the oversight of C. Le Prell with funding and clinical trial material provided by Edison Pharmaceuticals, Inc. Colleen Le Prell consults with various pharmaceutical companies engaged in the development of novel agents with potential auditory applications on an ongoing basis.

CONFLICT OF INTEREST

None.

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