FORUM REVIEW ARTICLE

Prevention of Noise-Induced Hearing Loss Using Investigational Medicines for the Inner Ear: Previous Trial Outcomes Should Inform Future Trial Design

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Abstract

Significance: Noise-induced hearing loss (NIHL) is an important public health issue resulting in decreased quality of life for affected individuals, and significant costs to employers and governmental agencies.

Recent Advances: Advances in the mechanistic understanding of NIHL have prompted a growing number of proposed, in-progress, and completed clinical trials for possible protections against NIHL *via* antioxidants and other drug agents. Thirty-one clinical trials evaluating prevention of either temporary or permanent NIHL were identified and are reviewed.

Critical Issues: This review revealed little consistency in the noise-exposed populations in which drugs are evaluated or the primary outcomes used to measure NIHL prevention. Changes in pure-tone thresholds were the most common primary outcomes; specific threshold metrics included both average hearing loss and incidence of significant hearing loss. Changes in otoacoustic emission (OAE) amplitude were relatively common secondary outcomes. Extended high-frequency (EHF) hearing and speech-in-noise perception are commonly adversely affected by noise exposure but are not consistently included in clinical trials assessing prevention of NIHL.

Future Directions: Multiple criteria are available for monitoring NIHL, but the specific criterion to be used to define clinically significant otoprotection remains a topic of discussion. Audiogram-based primary outcome measures can be combined with secondary outcomes, including OAE amplitude, EHF hearing, speech-in-noise testing, tinnitus surveys, and patient-reported outcomes. Standardization of test protocols for the above primary and secondary outcomes, and associated reporting criterion for each, would facilitate clinical trial design and comparison of results across investigational drug agents. *Antioxid. Redox Signal.* 36, 1171–1202.

Keywords: noise-induced hearing loss, NIHL, otoprotection, clinical trial, primary endpoint

Introduction

NOISE-INDUCED HEARING LOSS (NIHL) is a significant clinical issue. It is well known to impact those who work in loud occupational settings (76, 77, 178, 179), members of the armed forces (41, 56, 196), and musicians and other performing artists (67, 181, 191). Diagnosis of NIHL requires a history of noise exposure and hearing loss documented using pure-tone threshold testing (*i.e.*, the audiogram). Occupational NIHL is most commonly charac-

terized by a notched audiometric configuration in which hearing is poorer at 3, 4, or 6 kHz than at the lower frequencies (0.5, 1, and 2 kHz), with hearing recovering at 8 kHz relative to the poorest of the 3, 4, and 6 kHz frequencies (*e.g.*, 29, 147, 153). In contrast, it was recently suggested that military NIHL (M-NIHL) might be less notch-like, with hearing loss commonly observed at 8 kHz as well as 3, 4, and 6 kHz (124, 125).

Testing at 8 kHz is neither required nor precluded within the United States (U.S.) Department of Defense (DoD)

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Instruction 6055.12 (33). Prevalence of M-NIHL as defined by Moore (124) has not been described for U.S. service members at this time; however, tinnitus and hearing loss are two of the most prevalent service-connected disabilities for U.S. Veterans (183).

Within the U.S. civilian population, $\sim 25\%$ of the U.S. adults sampled in the 2011–2012 nationally representative National Health and Nutrition Examination Survey (NHANES) study had notched audiometric configurations potentially consistent with noise-induced injury [using a definition of a notch that includes a 15 dB deficit at 3, 4, or 6 kHz; see Carroll *et al.* (25)]. The World Health Organization (WHO) criterion for disabling hearing loss is 41 dB HL or poorer pure-tone average (PTA) threshold at 1, 2, 3, and 4 kHz (PTA1234). Some 16% of disabling hearing loss has been suggested to be attributable to occupational noise exposure at the global level, with $\sim 7\%$ of disabling hearing loss in North America being attributed to noise exposure [see also the recent review by Graydon *et al.* (42) and Nelson *et al.* (140)].

The WHO also reports some 1.1 billion young people worldwide may be at risk of NIHL based on both personal audio system (PAS) use and exposure to amplified music in bars, clubs, and concerts (195). The large number of individuals at risk of or already affected by NIHL has driven tremendous interest in investigational medicinal products for the inner ear. The U.S. Department of Defense Hearing Center of Excellence has accordingly been highly active in sponsoring open-access peer-reviewed content related to NIHL and its prevention, with many of their efforts led through the Pharmaceutical Interventions for Hearing Loss (PIHL) committee [for summary of open-access content, see Le Prell *et al.* (103)].

Although the notched audiogram is the primary clinical diagnostic tool for identification of NIHL, it is not the only test used to measure cochlear noise injury. In addition to the audiogram, distortion product otoacoustic emissions (DPOAEs), transient evoked otoacoustic emissions (TEOAEs), extended high-frequency (EHF) hearing thresholds, hearing-in-noise, evoked potentials, and a variety of qualitative hearing and tinnitus survey tools are used in research studies investigating noise injury. Clinical trials are different from basic discovery research; however, in that they emphasize the measurement of clinically significant drug benefits. To advance discussions about clinical trial outcomes appropriate for use in NIHL otoprotection clinical trials, this report first introduces test metrics of potential interest (DPOAEs, TEOAEs, EHF thresholds, hearing-in-noise) based on their use in basic research, and then describes regulatory considerations related to use of these tests in clinical trials.

Otoacoustic emissions (OAEs) provide a measurement of outer hair cell (OHC) function and provide an excellent example of a metric with widespread use in NIHL research but some limitations. OAEs are widely used in NIHL research based on the vulnerability of the OHCs to noise injury combined with evidence that significant OHC loss can accrue before measurable audiometric threshold shift. DPOAEs have been proposed for inclusion in hearing conservation programs (82) and clinical trials (81).

DPOAE thresholds can be measured in the same way that audiometric thresholds are determined; stimulus levels are systematically decreased until the DPOAE is no longer dis-

tinguishable from the noise floor, with threshold defined as the lowest stimulus level at which a reliable DPOAE is induced. Alternatively, DPOAE amplitude can be reported in either dB SPL or dB relative to the noise floor for stimuli presented at specific frequencies and sound levels.

DPOAE amplitude is routinely evaluated in clinical and research settings, with the measured response amplitude compared against published norms or other equipment-specific proprietary norms. However, the specific frequencies tested and the sound levels at which the eliciting frequencies are presented vary across clinical and research settings, in addition to variable choice of metrics such as threshold, amplitude, and amplitude relative to noise floor. During clinical evaluation of DPOAE amplitude, DPOAE responses are commonly categorized as within normal limits, present but abnormal (reduced amplitude), or absent, whereas research studies often include quantitative data rather than categorical data.

A second type of OAE that is commonly measured clinically and in research studies is the TEOAE. Both DPOAEs and TEOAEs provide simple, efficient, noninvasive, objective indicators of OHC function, but TEOAEs assess OHC function through ~ 5–6 kHz, whereas DPOAEs can assess function through ~ 16 kHz, depending on the specific commercial equipment options (75, 161). In addition, the TEOAE response is typically absent at frequencies at which hearing thresholds exceed 20–30 dB HL, whereas DPOAE responses can be recorded in patients or participants with thresholds up to ~ 40 dB HL (75).

During administration of ototoxic drugs, OAE amplitude is commonly observed to decrease before the development of measurable threshold shift, particularly when OAEs are measured at high frequencies [for review, see Campbell and Le Prell (20)]. Because OAE changes often precede overt threshold shift, the functional significance of OAE changes can be unclear, even though they serve as a reliable biomarker for OHC pathology.

A second hearing test that has been used clinically and in research investigating the effects of noise on the inner ear is EHF audiometry. Recent clinical guidance from the American Academy of Audiology (AAA) recommends EHF audiometry be used during audiometric monitoring of musicians and other performing artists (4). A variety of recent research studies investigating the earliest effects of noise injury have noted EHF threshold deficits in the absence of hearing loss within the conventional frequency range. Deficits have been observed in individuals who have diverse lifetime noise exposure histories, including music students, frequent concert goers, those with higher lifetime noise exposure, and youth shooters (46, 91, 111, 157). Thus, EHF audiometry, from 9 to 20 kHz, may be more sensitive to noise injury than threshold tests at frequencies through 8 kHz. As noted for OAE metrics, however, the functional significance of EHF threshold deficits is not necessarily clear.

A third functional assessment used in studies measuring noise injury is word recognition (in earlier terminology referred to as speech discrimination). These tests are conducted in quiet listening conditions. However, there are multiple variants of word recognition tests in which hearing-in-noise ability is measured using either word or sentence-based tests conducted against babble or other noise backgrounds at various signal-to-noise ratios (SNRs). Hearing-in-noise tests

in workers exposed to occupational noise and other diverse noise-exposed populations commonly reveal deficits with noise-exposed individuals requiring a higher SNR to correctly identify the target words [for review, see Le Prell (93) and Le Prell and Clavier (99)].

Difficulty understanding speech in noisy environments is the most commonly hypothesized functional effect of noise-induced neuropathic damage [(87, 113, 118, 154), see also the detailed discussions by Plack *et al.* (155, 156)]. However, OHC damage is also associated with speech-in-noise deficits [see, *e.g.*, Hoben *et al.* (62), Leger *et al.* (110), Parker (152), Summers *et al.* (174)]. Taken together, it is not yet clear if hearing-in-noise tests can distinguish deficits due to OHC death *versus* deficits due to neural pathology, but hearing-in-noise tests do appear to provide a compelling functional tool that is sensitive to noise-induced cochlear injury.

Recent years have brought an increasing interest in the use of sound evoked potentials, in the form of electrocochleography or the measurement of the auditory brainstem response (ABR), as tools for exploring effects of noise on the human inner ear. ABR wave I amplitude provides broad insight into the health of the inner hair cells (IHCs), the auditory nerve fiber (ANF) population, and the synapses connecting the IHCs to the ANFs, all of which must be intact for Wave I to be normal.

Studies in animal models revealed the synaptic connections between IHCs and ANFs to be highly vulnerable, with damage occurring after noise exposure that results in temporary threshold shift (TTS), even in the absence of permanent threshold shift (PTS) (61, 87). Evidence of noise-induced cochlear synaptopathy has been inconsistent in studies enrolling human participants [for review, see Bramhall *et al.* (15) and Le Prell (93)], although evidence consistent with age-related synaptopathy has been provided (70, 88). There are ongoing efforts in this area, and new data continue to emerge regarding age- and/or noise-induced cochlear synaptopathy (22, 23, 26, 121, 122).

Clinical trials are different from basic discovery research, in that they emphasize the measurement of clinically significant drug benefits. While the audiogram, DPOAEs, hearing-in-noise, EHF hearing, and electrophysiological measures are all well used within the research literature, the adoption of these different outcome measures in clinical trials on prevention of acquired hearing loss has varied across indications (i.e., NIHL, DIHL, sudden sensorineural hearing loss) [for review, see Le Prell (95)].

Even within NIHL prevention research, monitoring plans using the audiogram varied widely from study to study (95). The studies reviewed by Le Prell (95) were limited to clinical trials listed within the ClinicalTrials.gov database. Although this database provides good insights into drug development in the United States, many clinical trials were completed before the development of this database, and clinical research activities outside of the United States are not required to be listed at ClinicalTrials.gov. For this report, systematic data on the specific outcome measures used in NIHL otoprotection clinical trials were collected using both ClinicalTrials.gov and an additional search of the peer-reviewed literature to fully characterize the state of the science for NIHL otoprotection. Systematic outcome data are necessary to facilitate standardization of protocols to be used for evaluating efficacy of investigational medicinal products for NIHL prevention.

Calls for standardization of outcome measures in research and clinical testing are not new. As discussed by Schilder *et al.* (165), the choice of outcome measures for evaluating novel hearing therapeutics is a major issue with a need for consensus from industry, scientists, clinicians, and regulatory agencies.

Schilder *et al.* (165) describe several existing frameworks for standardization, including the Core Outcome Measures in Effectiveness Trials (COMET), Consensus-based Standards for the selection of health Measurement Instruments (COSMIN), and Centre for Outcomes Research and Evaluation (CORE). Their team developed core tinnitus outcome measures using COMET methodology as described in Hall *et al.* (51). The COMET initiative defines a Core Outcome Set as ''an agreed standardized set of outcomes that should be measured and reported, as a minimum, in all clinical trials in specific areas of health or health care.'' To facilitate the development of core outcomes in NIHL otoprotection research, a comprehensive search was used to identify the extent to which standardized outcomes currently do or do not exist for NIHL otoprotection studies.

At this time, no drugs have been approved by the U.S. Food and Drug Administration (FDA) for NIHL prevention. Indeed, the majority of the clinical trials described within the peer-reviewed literature do not appear to have been completed under the oversight of the FDA. FDA oversight is required to obtain regulatory approval in the U.S. Within the FDA, the Center for Drug Evaluation and Research (CDER) oversees the research, development, manufacture, and marketing of prescription, over-the-counter, and generic drugs to assure they are effective, with health benefits that outweigh potential adverse side-effects.

The FDA provides a wealth of information on the CDER website, but the process can be broadly generalized into two phases: first, CDER oversees drug developers' plans for manufacturing and testing *via* the Investigational New Drug (IND) application process. Second, CDER reviews completed reports to evaluate the data collected, assess relative benefits and risks, and make decisions regarding labeling to assure that the labeling accurately reflects health benefits and risks. During this confidential process, very little information is publicly available, as the FDA is specifically prohibited from releasing information on any drug under development, review, or pending approval, unless the information has been made public.

Although drug and study information is not available from the FDA, 42 CFR Part 11 requires clinical trials meeting specific criteria to register with the ClinicalTrials.gov databank (www.ClinicalTrials.gov). While 42 CFR 11.22 should be consulted for specific detail, the requirements broadly include registration for any U.S. clinical trial with one or more arms that (i) is interventional, (ii) is other than Phase 1, and/or (iii) studies an FDA-regulated drug product. The criteria for U.S. clinical trials further include (i) having at least one clinical trial location within the U.S. or one of its territories, (ii) product manufacturing in and export from the U.S. or one of its territories for study in another country, and/or (iii) the clinical trial has an FDA IND Number.

Based on the above criteria, any clinical trial investigating an intervention for hearing loss with a trial site in the U.S. or product manufacturing in the U.S. would likely be required to be listed on www.ClinicalTrials.gov. The regulatory

agencies in other countries have similar reporting requirements for studies within their borders. Unfortunately, a single repository listing all clinical trials investigating a given health issue, such as hearing loss, is not available.

As data supporting the potential use of investigational drug agents for prevention of hearing loss have emerged, interest in the regulatory process has grown (30, 54). To facilitate translational research activities including development and testing under an IND, Lynch *et al.* (117) provided a comprehensive summary of the IND process for agents that may ameliorate or prevent NIHL. In that same edition is a contribution from Staecker *et al.* (169), discussing the regulatory process for novel molecular therapeutics promoting regeneration and recovery of function. A major topic that remains unclear, however, is the selection of clinical trial outcomes, which can include the audiogram, DPOAEs, TEOAEs, EHF hearing, hearing-in-noise, evoked potentials, or tests other than those introduced above, such as patient-reported outcome measures (PROMs).

PROMs include widely used surveys such as the Hearing Handicap Inventory for Adults (HHIA) (143, 144) and the Hearing Handicap Inventory for the Elderly (HHIE) (186), as well as newer surveys, such as the Otology Questionnaire Amsterdam (84). Another example of a PROM is the Listening Effort Questionnaire-Cochlear Implant, described as "the first PROM to be developed specifically for the measurement of perceived listening effort" (57). The recent systematic literature review on PROMs for otologic complaints, by Viergever *et al.* (187), identified 33 tinnitus questionnaires, 23 vertigo questionnaires, 84 hearing loss questionnaires, and 15 multiple complaint questionnaires. Thus, there are many PROMs that could be included in clinical trials.

Attention to PROMs is significantly increasing, as the FDA recently permitted the Hearing Loss Association of America (HLAA) to convene the Externally Led Patient-Focused Drug Development Meeting. Representing the FDA, Dr. Gavin Imperato, medical officer within the Office of Tissues and Advanced Therapies within the FDA Center for Biologics, Evaluation, and Research, noted the critical importance of patient-focused drug development (see HLAA website for meeting transcript and recorded materials).

Methods

A PubMed search strategy using a variety of search terms was completed, using terms such as "NIHL otoprotection," "NIHL prevention," "PTS otoprotection," "PTS prevention," "TTS otoprotection," and "TTS prevention." In addition, multiple other literature reviews were searched for additional clinical trial references that might have been missed during the PubMed search process (including 48, 55, 94, 105, 107, 109, 149, 167, 185). All English-language studies identified *via* either PubMed or the inspection of published literature reviews were acquired and carefully reviewed, not only to extract study-specific information but also to identify any additional cited clinical trial reports. Clinical trials published in other languages [see, *e.g.,* Ge *et al.* (40)] were not systematically captured and are not included in this review.

In addition to the literature search described above, which identified completed clinical trials published in English, www.ClinicalTrials.gov was searched on December 3, 2020, to identify active and planned clinical trials as well as clinical trials that were completed but were not described in the peer-reviewed literature at the time of the search. Clinical trial listings were searched using the terms "noise induced hearing loss," "permanent threshold shift," and "temporary threshold shift." Results were cross-checked against the studies listed in Le Prell (94, 95) to confirm that studies identified previously were not missed. While the PubMed search captures all international research efforts published in English, the studies posted on ClinicalTrials.gov primarily reflect U.S. studies initiated since 2007. 42 CFR Part 11 only applies to clinical trials initiated after September 27, 2007, and as noted above, does not capture studies outside the U.S. unless the investigational medication is manufactured in the U.S. This search was updated on June 11, 2021, capturing several new studies posted on ClinicalTrials.gov subsequent to the initial search.

All clinical trials identified through the peer-reviewed literature search and the review of ClinicalTrials.gov study listings were sorted into four categories, including (i) prevention of PTS *via* prenoise therapy (Table 1); (ii) prevention of PTS *via* postnoise therapy (Table 2); (iii) prevention of TTS *via* prenoise therapy (Table 3); and (iv) prevention of TTS *via* postnoise therapy (Table 4). Studies that did not fit in any of the above categories included Phase 1 safety studies, nondrug educational interventions (videos, pamphlets, websites, *etc.*), retrospective analyses, studies evaluating prevention of tinnitus, studies evaluating hearing loss attributed to factors other than noise (aging, sudden hearing loss, *etc.*), or other studies that did not meet inclusion criteria, including use of an investigational medicinal product for NIHL prevention. Those studies are not discussed further here.

The overarching purposes of the current review were to (i) provide information about clinical trial populations in which drug interventions can be evaluated, a major challenge discussed by Le Prell *et al.* (102); and (ii) provide insight into feasible clinical trial outcomes, a major challenge discussed by Schilder *et al.* (165). Therefore, for each study belonging to one of the categories of interest, the study population and observed changes in hearing in untreated or placebo control conditions were documented, and the primary outcome measure and any secondary outcome measures were extracted.

With respect to the definition of outcome measures, the listings on ClinicalTrials.gov require outcome measures to be clearly specified as primary, secondary, or other. In contrast, many of the peer-reviewed reports do not clearly differentiate primary, secondary, and other outcomes. If outcomes were distinguished as primary or secondary in the peer-reviewed reports, they were identified accordingly. If the outcomes were not specifically identified as primary or secondary in the peer-reviewed report, efforts to infer the primary outcome from the descriptions within the statistical analysis plan, order of presentation in the methods and results, and order of discussion were made. If the study outcomes were not able to be distinguished with respect to relative importance (primary *vs.* secondary), they were listed within the tables as coprimary outcomes.

While the focus of this review is not the specific agents under evaluation, interventions are briefly described in Tables 1–4. As seen in the tables, many agents investigated to date have an antioxidant mechanism of action, although

TABLE 1. PERMANENT THRESHOLD SHIFT PREVENTION (PRENOISE ONSET OF TREATMENT)

Study ID and/or publication	Phase and location	Population and inclusion criteria	Intervention	Primary auditory outcomes	Secondary auditory outcomes	Observed hearing loss in control/placebo condition	Results
NCT0290335 (134); Campbell (18)	3 Fort Jackson, South Carolina	Drill Sergeant instructor trainees completing 11 days weapons training, including minimum of 500 rounds of M16 weapons fire (Fort Jackson); targeted enrollment was 600; n=260 participants in interim analysis (sex not reported) 21–45 years old Normal tympanometry PTA512 ≤40 dB HL Air-bone gaps ≤10 dB HPDs worn	D-methionine (oral); 100 mg/kg/day D-methionine delivered for 3 days before training, during 11 days of training, and for 4 days post-training	1. Change in pure-tone thresholds measured by absolute change and frequency of STS at days 15–16 2. Absolute threshold change and frequency of STS at day 22	1. Change in tinnitus loudness/annoyance days 15–16 2. Change in tinnitus loudness/annoyance at day 22 3. Tympanometric change from baseline	1. ASHA SOC in either ear: 15% 2. DOEHRSHC STS: 1.5% 3. DOEHRSHC Early Warning: 7.4%	Terminated; no results posted. Per final report to Army, lower than expected rate of STS and very low rate of tinnitus
NCT04768569 (138)	2 Washington University in St. Louis, Missouri	Scheduled to undergo skull-based surgery that requires ~1h of surgical drilling; planned enrollment=180 (M and F) ≥18 years old Normal tympanometry 0.5–3 kHz ≤25 dB HL; 4 kHz ≤30 dB HL; 6–8 kHz ≤45 dB HL Asymmetry <10 dB at 0.5–4 kHz	100 mg Zonisamide administered 4 h preoperative (or 4–12 h postoperative, see Table 2)	PTS ≥10 dB at any frequency from 2 to 6 kHz	1. Permanent change in DPOAE amplitude 2. Rate of NIOSH STS 3. PTS >15 dB at EHF 4. ECochG amplitude, latency, width 5. Change in SNR on WIN test	Not available	Not yet recruiting
Kopke et al. (83)	"Phase-2 like" Camp Pendleton, California	16 days weapons training; every participant fired 325 M16 rounds during training; participants also exposed to steady-state noise and simulated explosions (Camp Pendleton); 566 participants completed study, all M 18–35 years old Normal tympanometry 2–6 kHz ≤25 dB HL Asymmetry <30 dB at 8 kHz HPDs worn	N-acetylcysteine effervescent tablets 900 mg NAC t.i.d. for the first 13 days of training; on last 3 days of training delivered as 1800 mg a.m. dose and 900 mg p.m. dose	ASHA SOC in either ear	1. Mean change in threshold for left, right, and both ears 2. Rate of ASHA SOC in trigger-hand ear 3. Rate of modified Navy STS in trigger-hand ear 4. Tinnitus loudness and severity (TSI)	1. Average change in hearing ranged from +1.0 to −1.0 dB from 2 to 20 kHz 2. ASHA SOC in either ear: 38% 3. ASHA SOC in right ear: 27% 4. ASHA SOC in trigger-hand ear: 28% 5. Navy STS in trigger-hand ear: 35% 6. ASHA SOC in right ear for right-handed shooters: 28% 7. Navy STS in right ear for right-handed shooters: 36%	Subset of secondary and post hoc ancillary analyses revealed small but statistically significant reductions in NAC group; DPOAE differences were sporadic with respect to ear and frequency
Attias et al. (7); second analysis of study described in Joachims et al. (68)	See Joachims et al. (68)			Incidence of threshold >25 dB HL at one or more frequencies from 2 to 8 kHz	Severity of threshold shift at frequencies from 3 to 8 kHz reprinted from Joachims et al. (68)	Thresholds >25 dB HL post-training in 21.5% of left ears and 28.5% of right ears	Incidence of threshold shift >25 dB decreased to 11.2% in Mg group

TABLE 1. (CONTINUED)

Study ID and/or publication	Phase and location	Population and inclusion criteria	Intervention	Primary auditory outcomes	Secondary auditory outcomes	Observed hearing loss in control/placebo condition	Results
Joachims et al. (68)	N/A Negev Desert training camp, Israel	8 weeks of 6 days/week military basic training; average of 420 shots from M16 rifle (Israeli Defense Force); $n=320$, all M 17.7–18.5 years old 1–8 kHz <20 dB HL 9% of placebo and 13% of Mg groups did not always wear HPDs	6.7 mmol magnesium aspartate in lemonade; average dose 387 ± 23 mg magnesium per day	Incidence of threshold shifts of 5, 15, and 25 dB HL at 3, 4, 6, and 8 kHz in right and left ears	Changes in erythrocyte magnesium concentration	1. 5 dB threshold shift in 65%–70% of ears 2. 15 dB threshold shift observed in 20%–30% of ears 3. 25 dB threshold shift observed in <10% of ears	Incidence of threshold shifts >10 dB decreased by 50% in Mg group

ASHA SOC: ≥20 dB shift at any one test frequency or ≥10 dB shift at any two consecutive test frequencies; loss of response at 3 consecutive frequencies where response obtained at baseline.
Modified Navy STS: ≥15 dB shift at any one test frequency, or ≥10 dB shift at any two consecutive test frequencies.
DOEHRSHC STS: ≥10 dB average shift at 2, 3, and 4 kHz (identical to OSHA STS).
DOEHRSHC Early Warning: ≥15 dB shift at 1, 2, 3, or 4 kHz in either ear.
NIOSH STS: ≥15 dB shift at any test frequency from 0.5 to 6 kHz [1972 NIOSH criteria: ≥10 dB shift at 0.5, 1, 2, or 3 kHz; ≥15 dB shift at 4 or 6 kHz].

a.m., ante meridiem (before noon, indicates morning dose); ASHA SOC, Significant Ootoxic Change as defined by the American Speech-Language-Hearing Association; DOEHRSHC, Defense Occupational and Environmental Health Readiness System—Hearing Conservation; DPOAE, distortion product otoacoustic emission; EHF, extended high frequency; F, female; HPD, hearing protection device; M, male; NIOSH, National Institute of Occupational Safety and Health; OSHA, Occupational Safety and Health Administration; p.m., postmeridiem (after noon, indicates afternoon/evening dose); PTA, pure-tone average; PTS, permanent threshold shift; SNR, signal-to-noise ratio; STS, significant threshold shift; t.i.d., ter en die, three times a day; TSI, Tinnitus Severity Index; WIN, Words-in-Noise.

TABLE 2. PERMANENT THRESHOLD SHIFT RECOVERY OR REPAIR (POSTNOISE ONSET OF TREATMENT)

Study ID and/or publication	Phase and location	Population and inclusion criteria	Intervention	Primary auditory outcomes	Secondary auditory outcomes	Observed hearing loss in control/placebo condition	Results
NCT04768569 (138)	2 Washington University in St. Louis, Missouri	Scheduled to undergo skull-based surgery that requires ~1 h of surgical drilling; planned enrollment 180 (M and F) ≥18 years old. Normal tympanometry 0.5–3 kHz ≤25 dB HL; 4 kHz ≤30 dB HL; 6–8 kHz ≤45 dB HL. Asymmetry <10 dB at 0.5–4 kHz	100 mg Zonisamide administered either 4 h pre- (see Table 1) or 4–12 h postoperatively	PTS ≥10 dB at any frequency from 2 to 6 kHz 30 days postsurgery	1. Change in DPOAE amplitude 2. Rate of NIOSH STS 3. PTS >15 dB at EHF 4. Change in ECochG amplitude, latency, width 5. Change in SNR on WIN test	Not available	Not yet recruiting
NCT04774250 (139)	2 University of Akron, Ohio	Police office scheduled for firearm training or certification session; planned enrollment 126 (M and F) ≥18 years old. Normal tympanometry 0.5–3 kHz ≤25 dB HL; 4 kHz ≤30 dB HL; 6–8 kHz ≤45 dB HL. Asymmetry <10 dB at 0.5–4 kHz. TTS >10 dB HL at 2, 3, 4, and/or 6 kHz required for randomization to treatment	100 mg Zonisamide administered postshooting if TTS positive (TTS ≥10 dB HL at 2, 3, 4, and/or 6 kHz)	PTS ≥10 dB at any frequency from 2 to 6 kHz 30 days postexposure	1. Rate of NIOSH STS 2. Change in DPOAE amplitude 3. PTS >15 dB at EHF 4. Change in ECochG amplitude, latency, width 5. Change in SNR on WIN test 6. Pharmacogenetic testing/phenotypic correlations	Not available	Not yet recruiting
Suckfuell et al. (173)	1/2 ENT clinics at Universities in Berlin, Germany and Munich, Germany	Patients with acute acoustic trauma after exposure to firecrackers in Berlin and Munich on New Year's Eve 2005/2006, treated within 24 h; n=11 enrolled patients (sex not reported) Age not reported At least 30 dB hearing loss at 4 and/or 6 kHz with the worse ear injected if both ears had hearing loss	AM-111 (intratympanic; 0.4 mg/mL or 2 mg/mL within 24 h after noise exposure)	Recovery of the hearing threshold level at day 30	1. Local tolerance of AM-111 2. Recovery of the hearing threshold level at day 3 3. Change in intensity of any tinnitus present at baseline	No untreated controls included; participants randomized within two treatment conditions.	ITT injections well tolerated; no significant differences in recovery of the two treated groups
Zhou et al. (197)	NA Changhai Hospital, Shanghai, China	≥40 dB HL at 2, 4, and 6 kHz measured 3 days to 2 weeks post-trauma (primarily fireworks and military training); n=53 (44M and 9F). Diagnosis of NIHL was due to fireworks (42%), military training (39%), music (9%), or other noise exposure (10%)	Methylpred nisolone; i.v. or i.v. plus ITI	1. ≥15 dB improvement at 2, 4, and 6 kHz 2. ≥15% improvement in SDS	None	No untreated controls included; participants randomized within two treatment conditions.	Threshold improvement ≥15 dB and SDS improvement ≥15% occurred in greater proportion of i.v. plus ITT group than i.v. only group
Chang et al. (27)	NA ROK Armed Forces Yangju Hospital, Yangju, Republic of Korea	≥30 dB HL at 2, 4, and 8 kHz measured 3 days to 2 weeks post-trauma (military drills in the Republic of Korea Armed Forces using Daewoo Precision Industries K2 rifle); n=19, all M	Oral ginkgo biloba plus prednisolone delivered i.v. or i.v. plus ITI	Average improvement at 2, 4, and 8 kHz	None	No untreated controls included; participants randomized within two treatment conditions.	Threshold gains were statistically greater in i.v. plus ITT group than i.v. only group; ITT drug benefit interacted with initial severity of hearing loss

SDS: assessed using phonetically balanced, monosyllabic, 50-word list at 40 dB above speech reception threshold or maximum comfortable level.
ITI, intratympanic injection; i.v., intravenous; NIHL, noise-induced hearing loss; SDS, speech discrimination score; TTS, temporary threshold shift.

TABLE 3. TEMPORARY THRESHOLD SHIFT (PRENOISE ONSET OF TREATMENT)

Study ID and/or publication	Phase and location	Population and inclusion criteria	Intervention	Primary auditory outcomes	Secondary auditory outcomes	Observed hearing loss in control/placebo condition	Results
NCT01444846 (130); Kil et al. (78)	2 University of Florida	Normal hearing young adults exposed to 4h of prerecorded music delivered by insert earphones (n=83; 43M, 40F) 18–31 years old Normal tympanometry 0.25–8 kHz ≤25 dB HL Air-bone gap ≤10 dB Asymmetry ≤15 dB	Ebselen (200, 400, or 600 mg dose, b.i.d.) for 2 days pre-exposure plus the day of exposure and 1 day post-exposure	Change in threshold 15-min postexposure	1. 50% reduction in mean TTS averaged across 3, 4, and 6 kHz 2. Mean threshold shift across 4, 6, and 8 kHz 3. Mean threshold shift across all tested frequencies from 0.25 to 8 kHz 4. Proportion of participants with TTS ≥10 dB at any frequency from 15 min to 3.25 h postexposure	1. 3.0 dB mean threshold shift across 4, 6, and 8 kHz 2. 2.6 dB mean threshold shift across all tested frequencies from 0.25 to 8 kHz 3. 60% of participants had TTS ≥10 dB at any frequency at 15-min postexposure	Completed, results submitted. Statistically significant dose-dependent reductions in the small observed TTS and rate of ≥10-dB STS decreased from 60% to ~25%–30% across dose groups
NCT00808470 (129); Le Prell et al. (101)	2 University of Florida	Normal hearing young adults exposed to 4h of prerecorded music delivered by insert earphones (n=70, 32M, 38F) 18–35 years old Normal tympanometry 0.25–8 kHz ≤25 dB HL Air-bone gap ≤10 dB Asymmetry ≤15 dB	500 mg vitamin C (magnesium ascorbate), 315 mg magnesium (Mg citrate, Mg stearate), 267 mg vitamin E (d-α-tocopherol acetate), 18 mg beta carotene for 3 days pre-exposure plus the day of exposure	Average threshold shift at 4 kHz in both ears	1. Threshold shift at individual frequencies from 250 to 8000 Hz 15 min postmusic 2. Tinnitus incidence, loudness, bothersomeness 3. DPOAE amplitude change	1. 3.4 dB mean threshold shift at 4 kHz 2. 1.0 to 2.7 dB mean threshold shifts at other tested frequencies from 0.25 to 8 kHz 3. 6/35 participants reported tinnitus 4. Frequency-specific DPOAE amplitude reductions	Completed, has results No reduction in TTS; no reduction in DPOAE amplitude shift; statistically significant increase in percentage of participants reporting tinnitus
NCT00552786 (128); Lin et al. (112)	2 National Taiwan University Hospital, Taipei, Taiwan	Male steel industry workers in Taiwan with daily noise exposure 88–89 dBA; 6 workers with hearing loss >50 dB HL were excluded from analysis (n=77; all M) 25–65 years old male, not exposed to organic solvents or polycyclic aromatic hydrocarbons	600 mg N-acetylcysteine (NAC) twice daily for 2 weeks	Average TTS at 3, 4, and 6 kHz (HF PTA)	Average temporary DPOAE threshold change at 3, 4, and 6 kHz	2.8 dB mean HF PTA threshold shift	Completed, has results Reduction in HF PTA TTS was small (from 2.8 to 2.5 dB) but statistically significant
NCT02257983 (132)	2 University of Florida	Normal hearing young adults, exposed to 4h of prerecorded music delivered by insert earphones (n=77; M and F eligible but distribution not reported) 18–30 years old Normal audiology examination	Vincerinone™ (EPI-743) 400 mg orally t.i.d.	Pure-tone audiometry	Time to recovery after acute noise exposure	Not available	Completed; results not posted
NCT02049073 (131)	1 Washington University in St. Louis, Missouri	Normal hearing young adults, exposed to 4h of prerecorded music delivered by insert earphones (targeted enrollment was 50 participants, M and F) 18–30 years old Normal hearing	Zonisamide: 100 or 200 mg orally for 2 weeks	Pure-tone hearing thresholds (particularly 2, 3, 4, and 6 kHz) 15-min postexposure	1. DPOAE 2. Tinnitus (THI) 3. Pure-tone hearing thresholds 75-, 135-, and 195-min postexposure	Not available	Withdrawn
NCT02049073 (131)	2 Washington University in St. Louis, Missouri	Normal hearing young adults ages 18–30, exposed to 4h of prerecorded music delivered by insert earphones (targeted enrollment was 50 participants, M and F) 18–30 years old Normal hearing	Methylprednisolone: 32 mg or 64 mg once orally	Pure-tone hearing thresholds (particularly 2, 3, 4, and 6 kHz) 15-min postexposure	1. DPOAE 2. Tinnitus (THI) 3. Pure-tone hearing thresholds 75-, 135-, and 195-min postexposure	Not available	Withdrawn

(continued)

TABLE 3. (CONTINUED)

Study ID and/or publication	Phase and location	Population and inclusion criteria	Intervention	Primary auditory outcomes	Secondary auditory outcomes	Observed hearing loss in control/placebo condition	Results
NCT02779192 (133)	2 Multi-site: University of Miami, Florida University of Kansas Medical Center Medical University of South Carolina University of Texas Southwestern	Adults' ages 18–50 with history of occupational or recreational noise exposure, exposed to calibrated sound challenge (targeted enrollment is 180 participants, M and F) Participants may not have current conductive hearing loss or middle ear effusion, cannot have used ototoxic medications within 60 days of enrollment, and cannot have a history of autoimmune ear disease or middle or inner ear surgery; no threshold-based inclusion or exclusion criteria listed	Ebselen (200 or 400 mg b.i.d.) for 7 days beginning 1 day pre-exposure	Reduction in the incidence of STS postexposure	Improvement in Words-in-Noise score postexposure	Not available	Not yet recruiting
NCT03834714 (135)	NA Multisite: Fort Rucker, Alabama University of Miami, Florida Wright-Patterson Air Force Base	Normal hearing adults exposed to continuous broadband noise up to 25% of the allowable daily dose of noise per the AFI 48–127 Occupational Noise and Hearing Conservation Program (targeted enrollment is 100 participants, M and F) 18–45 years old Normal tympanometry 0.5–8 kHz ≤25 dB HL Normal OAEs	Near-infrared light delivered *via* Earlight generation 1.4 device	Change in auditory threshold from 0.5 to 8 kHz, up to 365 days	1. Change in OAEs, up to 365 days 2. Change in CAP, up to 365 days	Not available	Recruiting
Doosti *et al.* (34)	NA University of Social Welfare and Rehabilitation Sciences, Tehran, Iran	Male textile industry workers in Tehran with unprotected daily noise exposure >85 dBA (no HPD use) (*n* = 48, all M) 18–50 years old Participants may not have a history of acoustic trauma, otologic disease, or conditions that affect hearing; no threshold-based inclusion or exclusion criteria listed	NAC 1200 mg/day or ginseng 200 mg/day for 14 days	Change in prework-shift hearing measurements at 4, 6, and 16 kHz before and after 14 days of treatment	1. Change in hearing at 0.5, 1, 2, and 8 kHz 2. Change in hearing at 10, 12.5, and 14 kHz	Change in prework shift hearing in the placebo condition was small (4 kHz: 2.5 dB; 6 kHz: 2.3 dB; 16 kHz: 2.8 dB) but statistically significant	Statistically significant reductions in the small observed TTS with either NAC or ginseng
Staffa *et al.* (170)	NA University of Siena, Siena, Italy	Adults' ages 20–40 exposed to monaural narrowband noise centered at 3 kHz for 10 min, at 90 dB HL; *n* = 30 (*n* = 30; 18M, 12F)	Oral food supplement containing water-soluble coenzyme Q10 (Q-Ter), Vitamins E, B1, B2, B6, and B12, choline, Ginkgo biloba	Duration of TTS at 3, 4, 6, and 8 kHz; within-subject crossover design	TTS at 2-min and 15-min postnoise measured at 3, 4, 6, and 8 kHz	Threshold shift was significant at 2 min (4 kHz: 20 dB; 6 kHz: 30 dB; 8 kHz: 25 dB) and 15 min (4 kHz: 10 dB; 6 kHz: 20 dB; 8 kHz: 15 dB) postnoise; the longest recovery time was 45 min; all participants reported tinnitus for 24 h	~5–10 dB decrease in TTS at 4, 6, and 8 kHz; longest recovery to baseline decreased from 45 to 30 min in Q-Ter condition; all participants completed untreated exposure initially; 25/30 participated in a second treated exposure
Quaranta *et al.* (160)	NA University of Bari "A. Moro," Italy	Normal hearing (<20 dB HL from 0.5 to 8 kHz) adults ages 20–30 exposed to 90 dB HL 3 kHz pure tone for 10 min (*n* = 30; 15M, 15F)	Alpha lipoic acid, 600 mg, 1 h pre-exposure or once daily for 10 days pre-exposure	TTS at 3, 4, and 6 kHz	Click-evoked TEOAE amplitude at 0.3 Pa	TTS was observed 2 min postexposure (3 kHz: 5.8 dB; 4 kHz: 10.4 dB; 6 kHz: 15.6 dB) and TEOAE amplitude decreased by 0.7 dB SPL	10-day pretreatment with alpha-lipoic acid reliably decreased TTS at 6 kHz (from 15.6 to 7.3 dB) and reliably decreased TEOAE deficits (from 0.7 to −0.2 dB SPL)

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TABLE 3. (CONTINUED)

Study ID and/or publication	Phase and location	Population and inclusion criteria	Intervention	Primary auditory outcomes	Secondary auditory outcomes	Observed hearing loss in control/placebo condition	Results
Le Prell et al. (104)	NA Swedish army bases, accessed by team members at Karolinska Institutet, Stockholm, Sweden	Normal hearing (≤25 dB HL from 0.25 to 8 kHz) adults, including officers in the Swedish military and Swedish military academy trainees completing training with 40 shots fired from an automatic machine-gun (Ksp-58) in a bunker over <1-min period wearing HPD (n=31; 27M, 4F)	500 mg ascorbic acid, 1949 mg magnesium citrate, 305 mg α-tocopherol acetate, 18 mg beta carotene for 3 days pre-exposure plus the day of exposure	Greatest audiometric threshold shift at 3, 4, or 6 kHz in either ear; within-subject crossover design	1. Threshold shifts at individual frequencies 2. Change in DPOAE amplitude 3. Change in psychoacoustic modulation transfer function (PMTF) thresholds 4. Tinnitus measures	No reliable effect of the shooting exercises on hearing thresholds at any postshooting test time; tinnitus only sporadically reported	Five of six participants with large (8–14 dB) TTS in the placebo condition had smaller TTS (≤6 dB) in the treated condition
Kapoor et al. (74)	NA Ministry of Defence, Timarpur, Delhi, India	Normal hearing male industrial Army Base Workshop workers with 5 h occupational noise exposure with LAeq ranging from 98.3 to 108.1 dBA; no HPD (n=40; all M)	Carbogen inhalant (5-min twice daily prework and once daily postwork for 6 days) and/or vitamin E (400 mg/day for 6 days)	TTS at individual frequencies from 0.125 to 8 kHz, measured immediately postshift	Changes in biomarkers of oxidative stress	Postshift TTS was greatest from 2 to 8 kHz (2 kHz: 3.8 dB; 3 kHz: 3.9 dB; 4 kHz: 4.9 dB; 6 kHz: 5.6 dB; 8 kHz: 6.2 dB); plasma total antioxidant status, SOD and GSH decreased; blood MDA increased	TTS reduced by carbogen and carbogen plus vitamin E; changes in oxidative stress biomarkers reduced by carbogen and carbogen plus vitamin E
Fetoni et al. (37)	NA Study site not specified; lead author affiliated with Catholic University of Rome, Italy	Normal hearing (≤20 dB HL from 0.125 to 8 kHz) young adult males ages 23–28 exposed to continuous open-field white noise for 15 min at 90-dB HL (n=20; all M)	coenzyme Q₁₀ tablet (CoQ-Ter®), 200 mg, once daily for 7 days pre-exposure	DPOAE amplitude for F2 values of 1001, 1257, 2002, 2515, 3174, 4004, 5042, and 6348 Hz	TTS at 0.125, 0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz	DPOAE amplitudes for F2 values of 3174, 4004, 5042, and 6348 Hz reduced at 1 and 16 h postexposure; TTS not reliably induced	DPOAE amplitude changes prevented
Kramer et al. (85)	NA Study site not specified; lead author affiliated with San Diego State University, California	Normal hearing (≤25 dB HL from 1 to 8 kHz) young adults ages 19–29 attending nightclub for 2 h; 2 h Lavg was 92.5–102.8 (average exposure across 8 groups with tests staggered across 2 evenings: 98.1 dBA) (n=31; 14M, 17F)	NAC, 900 mg, administered 30 min before club entry	1. Average TTS measured 5 or 20 min postclub exit 2. Average DPOAE amplitude measured 5 min or 20 min postclub exit		Mean TTS was greatest at 4 kHz; mean TTS at 4 kHz was 14 dB when tested 5 min after exiting club and 9 dB when tested 20 min after exiting club; greatest DPOAE deficits were at 5–6 kHz	No reliable prevention of TTS or DPOAE amplitude deficits was observed
Attias et al. (6)	NA Study site not specified; lead author affiliated with University of Haifa, Haifa, Israel, and Schneider Children's Medical Center, Petach Tikva, Israel	Normal hearing (≤20 dB HL from 1 to 8 kHz) males ages 16–37 years; monaural 90-dB SL white noise for 10 min (n=20, all M)	Magnesium, 122 mg daily for 10 days, delivered as magnesium aspartate in juice	1. TTS measured immediately postexposure with repeat testing until recovered 2. DPOAE amplitude changes 15 and 30 min postexposure	Mg blood levels	Largest TTS was 40 dB and 28% of ears had TTS ≥20 dB; in placebo and untreated control conditions, mean TTS was 10–15 dB at 3 kHz and 15–20 dB at 4, 6, and 8 kHz; DPOAE threshold shifts were ~5–7 dB from 2 to 6 kHz	Mg treatment reduced TTS and DPOAE threshold shift; return to baseline was more rapid in the Mg-treated condition
Quaranta et al. (159)	NA Study site not specified; lead author affiliated with University of Bari, Bari, Italy	Normal hearing (≤15 dB HL from 0.25 to 8 kHz) young adults ages 20–30 years; narrowband noise centered at 3 kHz, bandwidth of 775 Hz, 112 dB SPL×10 min (n=20, sex not reported)	Vitamin B₁₂ i.m. delivered as cyanocobalamin 1 mg daily for 7 days and 5 mg on the eighth day (before exposure)	TTS measured in the right ear at 1, 2, 3, and 4 kHz 2-min postexposure	Serum B₁₂ concentration	Average TTS was 2.9 dB at 1 kHz, 5.2 dB at 2 kHz, 16.6 dB at 3 kHz, and 21.5 dB at 4 kHz	TTS was significantly reduced at 3 and 4 kHz
Toppila et al. (182)	NA Study site not specified; lead author affiliated with Finnish Institute of Occupational Health, Helsinki, Finland	Male students 20–25 years of age at Tampere University; nightclub music; 92–94 dBA for 4 h (n=30, all M)	NAC, 400 mg 1 h before entering discotheque	1. TTS at 0.5, 1, 2, 4, and 8 kHz measured 2 min postexposure 2. Left ear DPOAE with and without contralateral inhibition 3. Left ear TEOAE	Balance assessments including reach test, target test, step test, cone test, and tunnel test	8.3-dB TTS left ear at 4 kHz, 10 dB TTS right ear at 4 kHz; 0–3 dB TTS at other frequencies	No statistically significant prevention against observed changes in any measure of hearing

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TABLE 3. (CONTINUED)

Study ID and/or publication	Phase and location	Population and inclusion criteria	Intervention	Primary auditory outcomes	Secondary auditory outcomes	Observed hearing loss in control/placebo condition	Results
Chaturvedi et al. (28)	NA Defence Institute of Physiology & Allied Sciences, Delhi Cantt, India	Normal hearing (from 0.25 to 8 kHz) male Army volunteers 22–28 years old; white noise at 100 dBA for 20 min ($n=12$, all M)	Carbogen (Inhalant) delivered during 20 min noise exposure	TTS at 4 kHz 2 min postexposure; within-subject crossover design	1. TTS at other tested frequencies 2. TTS at 4 kHz 20, 60, 90, and 120 min postexposure	1. 4 kHz TTS: 2 min: 22.5 dB; 20 min: 11.0 dB; 60 min: 6.7 dB; 90 min: 3.5 dB; 120 min: 1.8 dB 2. Average TTS$_2$: 1 kHz: 4.3 dB; 2 kHz: 11.1 dB; 3 kHz: 15.8 dB; 6 kHz: 15.3 dB; 8 kHz: 11.0 dB	TTS significantly smaller and TTS recovery significantly faster in carbogen group
Witter et al. (194)	NA Study site not specified; corresponding author affiliated with University of Tennessee at Knoxville, Tennessee	Normal hearing (≤20 dB HL from 0.5 to 4 kHz) volunteers 25–35 years old; 1 kHz pure tone at 100 dB HTL for 10 min ($n=5$; 2M, 3F)	Carbogen (Inhalant) beginning either 0.5, 1.5, or 2 h before noise exposure; atmospheric air condition tested in first two exposures; carbogen tested in third exposure session	TTS at 2 kHz; within-subject crossover design	TTS recovery time	TTS at 2000 Hz was ~18–19 dB 2 min postexposure and ~6–7 dB at 1 h postexposure, with complete recovery by 24 h postexposure	TTS at 2 min decreased by ~5–7 dB and recovery time decreased to 20–25 min for all three carbogen conditions
Joglekar et al. (69)	NA Study site not specified; corresponding author affiliated with Hinsdale Medical Center, Illinois	Normal hearing (≤20 dB HL from 0.5 to 4 kHz) volunteers 23–72 years old; 1 kHz pure tone at 100 dB SPL for 10 min ($n=12$; 6M, 6F)	100% oxygen or carbogen (Inhalant) during 10-min noise exposure; atmospheric air condition during first exposure; pure oxygen during second exposure; carbogen during third exposure	Mean TTS was primary outcome; unclear whether TTS is plotted at a single frequency or average across 0.5, 1, 2, and 4 kHz; within-subject crossover design	TTS recovery time	Preliminary studies showed no TTS at exposures <95 dB; small TTS at 95 dB; a single 105-dB exposure caused a 45-dB threshold shift requiring 96 h to recover. TTS was ~26 dB immediately postexposure in atmospheric air (20% oxygen)	TTS ~4 dB smaller in oxygen condition and ~7 dB smaller in carbogen condition; none of the conditions recovered to baseline within 25 min

CAP, compound action potential; OAE, otoacoustic emission; THI, Tinnitus Handicap Inventory.

TABLE 4. TEMPORARY THRESHOLD SHIFT (POSTNOISE ONSET OF TREATMENT)

Study ID and/or publication	Phase and location	Population and inclusion criteria	Intervention	Primary auditory outcomes	Secondary auditory outcomes	Observed hearing loss in control/placebo condition	Results
Lindblad et al. (114)	NA Study site not specified; corresponding author affiliated with Karolinska Institutet, Stockholm, Sweden	Officers in the Swedish military completing training with 40 shots fired from an automatic machine gun (Ksp-58) in a bunker over <2-min period wearing level-dependent earmuffs (control: $n = 23$, 21M, 2F; experimental: $n = 11$; sex not reported)	NAC, 200 mg, first dose immediately after exposure and second dose 1 h postexposure; third and fourth doses were administered the next morning at breakfast and 1 h after breakfast	Threshold shift at 1, 1.5, 2, 3, 4, 6, and 8 kHz 15-, 75-, 135-, and 195-min postexposure	1. Change in TEOAE amplitude 3 h postshooting 2. Change in psycho-acoustic modulation transfer function (PMTF) thresholds 3 h postshooting	No reliable TTS observed; PMTF thresholds were significantly poorer 3 h after the shooting exercises with little recovery at 24 h but complete recovery at 1 week postshooting	Shooting-induced changes in PMTF thresholds were prevented
Joglekar et al. (69)	NA Study site not specified; corresponding author affiliated with Hinsdale Medical Center, Illinois	Normal hearing (≤20 dB HL from 0.5 to 4 kHz) volunteers 23–72 years old; 1 kHz pure tone at 100 dB SPL for 10 min ($n = 8$, sex not reported)	Carbogen (Inhalant) administered for 30 min after noise exposure; atmospheric air condition delivered after first exposure; carbogen delivered after second exposure	Mean TTS was primary outcome; unclear whether TTS is plotted at a single frequency or average across 0.5, 1, 2, and 4 kHz; within-subject crossover design	TTS recovery time	TTS was ~27–28 dB immediately postexposure; TTS recovery time was ~28 min	Postnoise TTS recovery decreased to ~18 min in carbogen condition; TTS recovery time decreased to ~18 min in carbogen condition

drugs with other mechanisms of action are also being investigated. With respect to study phase, information was typically but not always specified in the listings on ClinicalTrials.gov; however, study phase was not frequently specified in the peer-reviewed literature.

If the study phase was not specifically indicated in the peer-reviewed report, the phase is reported as NA rather than assigning a study phase. Phase 1 studies evaluate safety, Phase 2 studies provide an initial assessment of efficacy as well as additional safety data, and Phase 3 studies are large studies that significantly contribute to New Drug Application (NDA) preparation, which includes efficacy data and requested drug labeling claims. Phase 3 studies are sometimes called pivotal trials because of their importance within the NDA. The final information in the summary tables is the status of the clinical trial within the online listing (*i.e.*, completed, recruiting, not yet recruiting, terminated, unknown) and a brief summary of any drug benefits identified either in the online results reporting or in the study publications.

Results

As shown in Tables 1–4, a wide variety of primary and secondary clinical trial outcomes have been used in studies on NIHL prevention. Obvious variation exists among studies regarding whether the study evaluated TTS or PTS prevention, and whether the intervention was first administered pre- or postnoise exposure. In addition to general design differences, the rate and degree of hearing loss and the primary and secondary outcomes vary from study to study. Study design and dependent variable selection are summarized in Table 5.

As seen in Table 5, more than half of the studies identified within the peer-reviewed literature (19/31; 61%) or other publications (1/31; 3%) had no corresponding ClinicalTrials.gov listing. Many of these studies were completed before the development of ClinicalTrials.gov and the 2007 posting requirement; other studies were conducted in other countries. Thus, it is not surprising that many of the published studies did not have corresponding listings in ClinicalTrials.gov.

Four studies were both listed on ClinicalTrials.gov and published, with publications found in either the peer-reviewed (3/31; 10%) or other (1/31; 3%) literature. Seven studies were listed on ClinicalTrials.gov but not published (one completed, one recruiting, four not yet recruiting, one withdrawn). Of the 24 total completed studies (*i.e.*, either published or listed on clinical trials as completed with or without results posted), 5 were PTS prevention studies (5/24; 23%) and 19 were TTS prevention studies (19/24; 79%). Of the five active and pending studies (*i.e.*, recruiting or not yet recruiting), three were PTS prevention studies (3/5; 60%) and two were TTS prevention studies (2/5; 40%). Thus, the data shown in Table 5 appear to show relatively equal proportions of new PTS and TTS prevention studies, a contrast to the relative preponderance of completed TTS studies within the published literature.

Of the 11 studies that had listings in ClinicalTrials.gov (7 listed, 4 listed and published), one study was Phase 1/2 (1/11; 9%), 9 studies were Phase 2 (9/11; 82%), and one study was Phase 3 (1/11; 9%). One additional peer-reviewed publication was described as Phase 2 like but was not listed on the

TABLE 5. SUMMARY OF CLINICAL TRIAL DESIGN DATA ACROSS PERMANENT THRESHOLD SHIFT AND TEMPORARY THRESHOLD SHIFT STUDIES WITH TREATMENT BEGINNING BEFORE AND AFTER THE ONSET OF EXPOSURE

	PTS pretreatment (n=4 trials[a])	PTS post-treatment (n=5 trials)	TTS pretreatment (n=20 trials)	TTS post-treatment (n=2 trials)	Total (n=31 trials)
Where located					
Peer-reviewed publication	2/4; 50%	3/5; 60%	12/20; 60%	2/2; 100%	19/31; 61%
Other publication	0	0	1/20; 5%	0	1/31; 3%
Listed at ClinicalTrials.gov	1/4; 25%	2/5; 40%	4/20; 20%	0	7/31; 23%
Both listed and published	1/4; 25%	0	3/20; 15%	0	4/31; 13%
Study status					
Completed, with results[b]	2/4; 50%	3/5; 60%	16/20; 80%	2/2; 100%	23/31; 74%
Completed, no results	0	0	1/20; 5%	0	1/31; 3%
Recruiting	0	0	1/20; 5%	0	1/31; 3%
Terminated	1/4; 25%	0	0	0	1/31; 3%
Not yet recruiting	1/4; 25%	2/5; 40%	1/20; 5%	0	4/31; 13%
Withdrawn	0	0	1/20; 5%	0	1/31; 3%
Unknown	0	0	0	0	0
Study phase					
1 (and 1/2)	0	1/5; 20%	1/20; 5%	0	2/31; 6%
2 (and Phase 2-like)	2/4; 50%	2/5; 40%	5/20; 25%	0	9/31; 29%
3	1/4; 25%	0	0	0	1/31; 3%
4	0	0	0	0	0
NA	1/4; 25%	2/5; 40%	14/20; 70%	2/2; 100%	19/31; 61%
Participant sex					
Male only	2/4; 50%	1/5; 20%	7/20; 35%	0	10/31; 32%
Male and female	1/4; 25%	3/5; 60%	11/20; 55%	0	15/31; 48%
Sex not reported	1/4; 25%	1/5; 20%	2/20; 10%	2/2; 100%	6/31; 19%
Study population					
Military/police weapons training	3/4; 75%	2/5; 40%	1/20; 5%	1/2; 50%	7/31; 23%
Fireworks	0	1/5; 20%	0	0	1/31; 3%
Fireworks or weapons training	0	1/5; 20%	0	0	1/31; 3%
Surgical drilling	1/4; 25%	1/5; 20%			2/31; 6%
Music exposure: earphones	0	0	5/20; 25%	0	5/31; 16%
Music exposure: club	0	0	2/20; 10%	0	2/31; 6%
Occupational noise (workers)	0	0	3/20; 15%	0	3/31; 10%
White noise	0	0	3/20; 15%	0	3/31; 10%
Broadband noise	0	0	1/20; 5%	0	1/31; 3%
Narrowband noise	0	0	2/20; 10%	0	2/31; 6%
Pure tone	0	0	3/20; 15%	1/2; 50%	4/31; 13%
Method of drug delivery					
Oral	4/4; 100%	0	15/20; 75%	1/2; 50%	21/31; 68%
Intratympanic injection	0	5/5; 100%	0	0	5/31; 16%
Inhalant	0	0	4/20; 20%	1/2; 50%	5/31; 16%
Infrared light device	0	0	1/20; 5%	0	1/31; 3%
Investigational drug agent					
Alpha-lipoic acid	0	0	1/20; 5%	0	1/31; 3%
AM-111	0	1/5; 20%	0	0	1/31; 3%
Carbogen	0	0	4/20; 20%	1/2; 50%	5/31; 16%
Coenzyme Q10	0	0	1/20; 5%	0	1/31; 3%
Coenzyme Q10 plus vitamins E, B1, B2, B6, and B12, choline, Ginkgo biloba	0	0	1/20; 5%	0	1/31; 3%
D-methionine	1/4; 25%	0	0	0	1/31; 3%
Ebselen/SPI-1005	0	0	2/20; 10%	0	2/31; 6%
EPI-743/Vincerinone	0	0	1/20; 5%	0	1/31; 3%
Magnesium	1/4; 25%	0	1/20; 5%	0	2/31; 6%
Methylprednisolone	0	1/5; 20%	1/20; 5%	0	2/31; 6%
N-acetylcysteine	1/4; 25%	0	4/20; 20%	1/2; 50%	6/31; 19%
Prednisolone (plus ginkgo biloba)	0	1/5; 20%	0	0	1/31; 3%
Vitamins A (beta-carotene), C, and E and magnesium	0	0	2/20; 10%	0	2/31; 6%

(*continued*)

	PTS pretreatment (n=4 trials[a])	PTS post-treatment (n=5 trials)	TTS pretreatment (n=20 trials)	TTS post-treatment (n=2 trials)	Total (n=31 trials)
Vitamin B12	0	0	1/20; 5%	0	1/31; 3%
Zonisamide	1/4; 25%	2/5; 40%	1/20; 5%	0	4/31; 13%
Inclusion as primary or coprimary outcome					
Average threshold shift	1/4; 25%	2/5; 40%	17/20; 85%	2/2; 100%	22/31; 71%
Duration of threshold shift	0	0	1/20; 5%	0	1/31; 3%
ASHA SOC	1/4; 25%	0	0	0	1/31; 3%
Other STS (unspecified)	1/4; 25%	0	1/20; 5%	0	2/31; 6%
Rate of threshold shift ≥25 dB	1/4; 25%	0	0	0	1/31; 3%
Rate of threshold shift ≥5, 15, or 25 dB	1/4; 25%	0	0	0	1/31; 3%
Rate of threshold shift ≥15 dB	0	1/5; 20%	0	0	1/31; 3%
Rate of threshold shift ≥10 dB	1/4; 25%	2/5; 40%			3/31; 10%
DPOAE amplitude	0	0	4/20; 20%	0	4/31; 13%
TEOAE amplitude	0	0	1/20; 5%	0	1/31; 3%
Word recognition change ≥15%	0	1/5; 20%	0	0	1/31; 3%
Inclusion as secondary outcome					
Average threshold shift	1/4; 25%	1/5; 20%	8/20; 40%	0	10/31; 32%
Duration of threshold shift	0	0	3/20; 15%	0	3/31; 10%
ASHA SOC	1/4; 25%	0	0	0	1/31; 3%
OSHA/DOEHRSHC STS	1/4; 25%	0	0	0	1/31; 3%
NIOSH/DOEHRSHC early warning	1/4; 25%	2/5; 40%	0	0	3/31; 10%
Modified Navy STS	1/4; 25%	0	0	0	1/31; 3%
Rate of threshold shift ≥10 dB	0	0	1/20; 5%	0	1/31; 3%
DPOAE amplitude	2/4; 50%	2/5; 40%	3/20; 15%	0	7/31; 23%
DPOAE threshold	0	0	1/20; 5%	0	1/31; 3%
DPOAE unspecified	0	0	1/20; 5%	0	1/31; 3%
TEOAE amplitude	0	0	1/20; 5%	1/1; 100%	2/31; 6%
EHF threshold	1/4; 25%	2/5; 40%	1/20; 5%	0	4/31; 13%
Hearing in noise	1/4; 25%	2/5; 40%	1/20; 5%	0	4/31; 13%
THI	0	0	1/20; 5%	0	1/31; 3%
Tinnitus incidence	0	0	3/20; 15%	0	3/31; 10%
Tinnitus loudness/annoyance	1/4; 25%	0	1/20; 5%	0	2/31; 6%
Tinnitus severity	1/4; 25%	0	0	0	1/31; 3%
Tinnitus intensity	0	1/5; 20%	0	0	1/31; 3%
CAP/ECochG	1/4; 25%	2/5; 40%	1/20; 5%	0	4/31; 13%
Balance tests	0	0	1/20; 5%	0	1/31; 3%
Tympanometric change	1/4; 25%	0	0	0	1/31; 3%
Psychoacoustic modulation transfer function	0	0	1/20; 5%	1/1; 100%	2/31; 6%

[a]Attias et al. (7) and Joachims et al. (68) provide two different analyses of a single clinical trial; the clinical trial was counted as a single study in all counts.

[b]Studies were defined as "Completed with results" if the data were provided on ClinicalTrials.gov or published in the peer-reviewed literature.

ClinicalTrials.gov website. Thus, the state of the science is primarily in the early phases of efficacy assessment with only one pivotal trial initiated to date.

Completed trials provide important insights into issues such as screening failures (i.e., inclusion criteria not satisfied), and suggest that study attrition can also be significant. For example, Kil et al. (78) screened 160 participants to obtain their final sample of 83, and Kopke et al. (83) screened 900 participants to arrive at their final sample size of 566.

Table 5 reports the number of participants completing the study and the sex distribution. About one-third of the identified studies reported male-only enrollment (10/31; 30%), and about half of the identified studies reported both male and female enrollment (15/31; 48%). The remaining studies did not report the distribution of participants with respect to sex or gender (6/31; 19%). Expectations regarding the inclusion of women (and children when appropriate) have increased,

and there is increased expectation that clinical trial participants will include members of diverse racial and ethnic groups. Thus, it is reasonable to predict more balanced designs in the future, although some noise-exposed populations are male biased, which may preclude balanced enrollment in some studies.

With respect to populations and exposure paradigms, the PTS otoprotection studies have predominantly enrolled or plan to enroll participants exposed to impulse noise (military weapons fire, firecrackers) (7/9; 78%), whereas only a small number of TTS otoprotection studies have enrolled or plan to enroll participants with exposure to impulse noise (2/22; 9%) (Table 5). As shown in Table 5, TTS otoprotection studies include some real-world exposures (weapons training, club music, occupational noise) and a variety of laboratory-based exposures (music, white noise, broadband noise, narrowband noise, pure-tone exposure).

Across PTS and TTS studies, the method of drug administration has primarily been oral (21/31; 68%). One study investigating the potential for "rescue" against PTS using a therapy initiated postnoise used intratympanic injection (ITI), and two steroid-based studies investigating postnoise rescue compared intravenous (i.v.) administered steroids (control) with i.v. steroids combined with ITI steroids (experimental). Five TTS studies investigated an inhalant approach (5/31; 16%), and one study is using infrared light, which is not a drug therapy but was included for completeness as it was the only investigational device-based approach.

Audiogram

Of 31 study reports listed in Tables 1 through 4, only one study did not use the audiogram as its primary outcome (37). However, the audiogram was included in the trial design, as changes in the audiogram were compared with changes measured using DPOAE amplitude. Notching of the audiogram generally was not included as a study variable. Instead, average threshold shift and/or the rate of threshold shift were the predominant measures across the various noise-exposed clinical trial populations. As shown in Table 5, trial designs showed significant variation in the participants' exposure, primary outcome selection, and rate at which hearing loss is reported.

Otoacoustic emissions

Table 5 shows that OAEs were included as a primary or coprimary outcome in 16% of clinical trials (5/31), and as a secondary outcome in 35% of the trials (11/31). The majority of the clinical trials reporting use of OAEs measured DPOAEs. TEOAEs were only monitored in three of the 16 trials reporting collection of OAE data (114, 160, 182).

EHF audiometry

Tables 1–4 show that EHF thresholds have been monitored in very few NIHL prevention studies (see also summary in Table 5). EHF hearing provided a secondary outcome in the clinical trial by Doosti *et al.* (34) and was included in the study by Kopke *et al.* (83), but EHF testing was not reported in any other clinical trial identified in this search. In Kopke *et al.* (83), they reported significant threshold shift (STS) protection in *post hoc* analyses, but a closer inspection reveals that they only had significant protection at 2 of 11 frequencies (8 and 18 kHz), which is of uncertain clinical importance. EHF thresholds will be measured as secondary outcomes in two new clinical trials that are not yet recruiting [NCT04768569 (138), NCT04774250 (139)].

Hearing in noise

Tables 1–4 revealed that inclusion of speech or speech-in-noise tests as primary or secondary endpoints in NIHL otoprotection trials is not common (see also summary in Table 5). One study reported improvement in word recognition scores (described by the authors as speech discrimination scores at 40 dB SL) as a coprimary endpoint (197). Three studies that are not yet recruiting will use word-in-noise test scores as a secondary outcome [NCT04768569 (138), NCT02779192 (133), NCT04774250 (139)].

Electrocochleography

Electrocochleography was only rarely noted in Tables 1–4 (see also summary in Table 5). It is used in NCT03834714 (135), which is currently recruiting participants into a study evaluating an investigational device: the Earlight. In addition, both NCT04768569 (138) and NCT04774250 (139), neither of which is recruiting yet, will include electrocochleography as a secondary outcome measure.

Tinnitus

In Tables 1–4, it can be seen that tinnitus was identified as a secondary outcome for a variety of studies, including both PTS prevention [NCT0290335 (134), reported in Campbell (18), and Kopke *et al.* (83)] and TTS prevention [NCT00808470 (129), reported in Le Prell *et al.* (101), NCT02049073 (131); Le Prell *et al.* (104)]. As summarized in Table 5, questions about tinnitus were included as a secondary outcome in 8 of the 31 clinical trials (26%). Several of these clinical trials measured tinnitus incidence (3/8; 38%), although there were also ratings of loudness and annoyance (2/8; 25%), severity (1/8; 13%), or intensity (1/8; 13%). Only one clinical trial used a validated survey (1/8; 13%), which was the Tinnitus Handicap Inventory (THI) developed by Baguley and colleagues (8–10).

Patient-reported outcome measures

No hearing-specific PROMs were reported in any of the investigations summarized in Tables 1–4.

Discussion

Le Prell and Miller (106) noted the tremendous variation in otoprotection research paradigms within animal models and noted the challenges this variation introduces when trying to make comparisons of the relative efficacy of different agents. The variation across preclinical research studies has since been carefully characterized in the systematic review by Hammill (53). To be able to draw inferences about the relative clinical efficacy of different otoprotective agents, it will be helpful if clinical trials not only share common endpoints but also use common definitions of what constitutes a clinically significant shift within each of those primary and secondary endpoints.

Clinical significance and statistical significance are both important. As discussed in Le Prell (92), preventing small changes in hearing does not clearly have clinical significance, even if the prevention is statistically significant. In many cases to date, the small observed reductions in hearing loss are directly related to the small changes observed in untreated or placebo control groups. If the placebo group exhibits small noise-induced threshold shifts, the investigational drug will show only small protective effects. Although clinical significance of such results (*e.g.*, prevention of small threshold shifts) is uncertain, such results are nonetheless encouraging in that they suggest the experimental medicine reached the inner ear in a biologically relevant dose. Nonetheless, such results do not assure that protection will extend to more robust noise exposure with greater injury to the cochlea.

The limited availability of clinical trial populations in which otoprotection can be investigated has been discussed in several recent reports (56, 102). In the remaining sections of

text, variation in outcome measures and observed noise injury across human otoprotection research study designs is discussed in detail to facilitate insights into clinical trial populations and clinically relevant study endpoints for those populations.

PTS trials with prenoise treatment onset: paradigms and observed PTS

As introduced above, studies investigating the prevalence of human NIHL have long used the audiogram as the primary clinical outcome, with evidence of a notched audiogram in combination with reported noise exposure being the gold standard for diagnosis of NIHL. Measurement of conventional (0.125–8 kHz) pure-tone thresholds within otoprotection investigations is thus well agreed (19, 20, 163). The vast majority of the studies identified here used the audiogram as the primary outcome.

Of the PTS prevention trials summarized in Tables 1 (pretreatment) and 2 (post-treatment), five included soldiers exposed to weapons fire (7, 18, 27, 68, 83, 197), one included safety officers exposed to weapons fire [NCT04774250 (139)], one included impulse noise produced by firecrackers (173), and one included patients exposed to drilling noise during otologic surgery [NCT04768569 (138)]. [The reports by Joachims *et al.* (68) and Attias *et al.* (7) provide two analyses of the same magnesium-treated clinical trial cohort, and NCT04768569 (138) is listed in both Tables 1 and 2, as it includes both a pretreatment arm and a post-treatment arm.]

While not the only source of noise exposure for soldiers, the hazards of auditory injury as a consequence of military weapon sound are well known (71), and the problem of NIHL in service members is significant (41, 56, 177, 196). Dangerously high sound levels are well documented during discharge of semiautomatic rifles [see, *e.g.*, Lobarinas et al. (115) and Meinke *et al.* (120)].

Data from a military population wearing unilateral hearing protection during weapons training, including 6 shots fired from a K-2 rifle or 10 shots from a K-5 revolver, revealed average thresholds of 6.5 dB in the hearing protection device (HPD)-protected ear *versus* 33.1 dB in the unprotected ear (123), suggesting that even a small number of unprotected firearm discharges can have significant effects on hearing. Given this, it is not surprising that those exposed to weapons fire have been the primary population recruited into PTS prevention studies.

The only Phase 3 clinical trial investigating PTS prevention listed in the ClinicalTrials.gov database is NCT0290335 (134) [described further in Campbell (18)]. This clinical trial was a randomized, placebo-controlled, double-blind trial evaluating oral D-methionine in Drill Sargent Instructor trainees, firing a minimum of 500 rounds from an M16 rifle over 11 days of weapons training. The subjects wore HPDs, reducing the noise exposure associated with weapons fire. The results provided in Campbell (18) are obtained from an interim, not final, analysis, and the study results have not yet been published in the peer-reviewed literature, but they nonetheless provide several insights into the challenges of NIHL otoprotection research.

One notable challenge is the less-than-expected rate of significant change in the control group. The lower than expected rate of STS increased projected enrollment requirements at the interim analysis, and expanding enrollment would have increased study costs beyond the funds available [as discussed in Campbell (18)].

Three additional PTS prevention reports, evaluating prevention of PTS with either N-acetylcysteine or magnesium treatment beginning before exposure, are available in the peer-reviewed literature (7, 68, 83). Both the N-acetylcysteine and magnesium studies were randomized, placebo-controlled, double-blind trials enrolling either Marine Corps trainees, firing a minimum of 325 rounds from an M16 rifle over 16 days of weapons training (83) or Israeli Defense Force trainees firing a minimum of 420 rounds from an M16 rifle over 2 months of basic training including weapons training (7, 68).

The primary outcomes specified in the online study listing for NCT0290335 (134) are ''Change in pure-tone thresholds measured by absolute change and frequency of STS at day 15–16'' and ''Absolute threshold change and frequency of STS at day 22.'' Although, as described in Campbell (18), the study was terminated early after interim analysis, Campbell (18) was nonetheless able to report the rate of STS using a variety of possible STS definitions.

STS was defined using the Significant Ototoxic Change (SOC) criteria of the American Speech-Language-Hearing Association (ASHA SOC: ≥20 dB shift at any one test frequency or ≥10 dB shift at any two consecutive test frequencies; loss of response at three consecutive frequencies where response was obtained at baseline) and following the Defense Occupational and Environmental Health Readiness System–Hearing Conservation (DOEHRSHC). The DOEHRSHC definition of STS is identical to Standard Threshold Shift as defined in 29 CFR 1910.95 (150), which includes ≥10 dB average shift at 2, 3, and 4 kHz. It is notable that <2% of the placebo group developed hearing loss meeting the DOEHRSHC/Occupational Safety and Health Administration (OSHA) STS criteria despite firing a minimum of 500 rounds of M16 weapons fire during the clinical trial.

Also reported in Campbell (18) were the DOEHRSHC Early Warning STS rates, defined as ≥15 dB shift at 1, 2, 3, or 4 kHz in either ear, a definition consistent with, but not identical to, the definition used by the National Institute of Occupational Safety and Health (NIOSH) (146), which defines STS as ≥15 dB shift at any test frequency from 0.5 to 6 kHz. DOEHRSHC Early Warning STS criteria were met by 7.4% of the placebo-treated participants. The rate of ASHA SOC was slightly higher, with 15% meeting the ASHA SOC criteria in at least one ear.

Because the rate of DOEHRSHC Early Warning shifts (≥15 dB shift at 1, 2, 3, or 4 kHz in either ear) was less than the rate of ASHA SOC (≥20 dB shift at any one test frequency or ≥10 dB shift at any two consecutive test frequencies), it is possible that a subset of participants may have had ≥20 dB shift at frequencies other than 1, 2, 3, or 4 kHz, or, 10 dB shifts at consecutive frequencies within the subset of frequencies most likely to be affected (*i.e.*, 3 and 4 kHz, or 4 and 6 kHz). Either of these patterns of shift would meet the ASHA SOC criteria but not the DOEHRSHC Early Warning criteria.

In contrast to the 15% meeting ASHA SOC criteria in Campbell (18), 38% of the participants in the clinical trial described by Kopke *et al.* (83) ASHA SOC criteria despite the smaller number of rifle rounds discharged. However, the population studied by Kopke *et al.* (83) had additional steady-

state noise exposure and simulated explosion exposures, making the exposures in the Camp Pendleton Marine Corp population recruited by Kopke *et al.* (83) and the Fort Jackson Army population recruited by Campbell (18) not directly comparable. In addition, the protocol used by Kopke *et al.* (83) included EHF threshold shifts, whereas the protocol used by Campbell (18) did not. If basal regions of the cochlea, responsible for EHF sensitivity, are more vulnerable to noise-induced injury, higher rates of ASHA SOC would be expected when testing includes EHF threshold measurements.

It is also possible that the different rates of ASHA SOC described in the placebo groups within the Campbell (18) and Kopke *et al.* (83) study reports are associated with differences in HPD use. Whereas the Kopke study enrolled new marine recruits, the Campbell study enrolled drill sergeant instructor trainees. Experienced soldiers may be more likely to be compliant with HPD use than new recruits participating in basic training.

Kopke *et al.* (83) did not report the rate at which DOEHRSHC STS and Early Warning criteria were met. They did however report the average shift in hearing at individual frequencies from 2 to 20 kHz, with small ($\sim$1 dB), but statistically significant, differences in threshold shift for both ears at 6 and 18 kHz, and for the right ear at 8 kHz. Kopke *et al.* (83) also reported the rate at which an adaptation of the STS criteria of the U.S. Navy was met, based on ≥15 dB shift at any one test frequency or ≥10 dB shift at any two consecutive test frequencies, with data reported for the left ear, right ear, either ear, both ears, trigger-hand ear, nontrigger-hand ear, and trigger- and nontrigger-hand ear within right- and left-handed shooter subgroups, with STS rates ranging from as low as 12% (ASHA SOC in right ear of left trigger-hand recruits) to as high as 53% (adapted Navy STS in either ear).

Statistically significant decreases were noted for 4 of the 16 *post hoc* subgroup analyses. However, no corrections for the multiple comparisons were applied. An alpha level of 0.05 was used to determine significance within the one-sided statistical tests.

Joachims *et al.* (68) did not report STS rates using the same criteria as the U.S. studies by Campbell (18) and Kopke *et al.* (83). Instead, they reported the percentage of participants with 5-, 15-, or 25-dB threshold shifts at 3, 4, 6, or 8 kHz, with some 20%–30% of participants developing ≥15-dB HL shift at one or more frequencies but <10% developing ≥25-dB HL shift after 8 weeks of basic training.

The relatively "lower than expected" rates at which NIHL has been documented in the completed prospective clinical trials using pretreatment paradigms are notable. Increased attention to HPD use during the clinical trials may have prevented STS in participants, including both those receiving placebo and those receiving the active agent. Documenting achieved HPD attenuation and consistency of HPD use by study participants should be considered as a possible strategy that may have the potential to improve the interpretation of drug efficacy in PTS prevention studies.

PTS trials with postnoise treatment onset: paradigms and observed PTS

For postnoise rescue (Table 2), three completed clinical trials evaluated prevention of PTS secondary to impulse noise, although none of the completed studies included an untreated or placebo control condition (27, 173, 197). Like the studies evaluating pretreatment (Table 1), the studies by Zhou *et al.* (197) and Chang *et al.* (27) enrolled military personnel exposed to weapons fire; however, participants were recruited when they sought medical intervention for hearing loss subsequent to weapons discharge.

Participants in the study by Zhou *et al.* (197), conducted at the Second Military Medical University in Shanghai, were eligible to participate if they had PTA thresholds ≥40 dB HL at 2, 4, and 6 kHz when measured from 3 days to 2 weeks post-trauma; hearing loss was largely attributed to fireworks (42% of participants) or military training (39% of participants). Once enrolled, participants were randomized to receive either i.v. methylprednisolone (control) or i.v. methylprednisolone in combination with intratympanic methylprednisolone. Significant recovery was defined as ≥15 dB average improvement at 2, 4, and 6 kHz, or ≥15% recovery of word recognition scores for words presented at a level 40 dB higher than the speech reception threshold (40 dB SL).

In the group receiving both i.v. and intratympanic steroids, 52% met the recovery criteria, which was statistically significantly greater than the 23% of i.v. steroid control participants who met the recovery criteria at 8 weeks post-treatment. A challenge in interpreting PTS rescue is that normal hearing before the acute trauma was assumed, which cannot necessarily be assumed in adults, particularly in the case of those serving in the military. Because partial or complete hearing recovery occurs in most individuals, studies without an adequate control group are difficult to interpret. Even with controls, the high variability in natural recovery and the usual variability in the natural noise exposures that triggered the hearing loss mean that large numbers of subjects may be necessary to adequately power the study and facilitate interpretation.

Participants in the study by Chang *et al.* (27) were eligible to participate if they had PTA thresholds ≥30 dB HL at 2, 4, and 8 kHz when measured from 3 days to 2 weeks post-trauma; hearing loss was due to military drills using the K2 rifle in the Republic of Korea Armed Forces. Once enrolled, participants were randomized to receive either oral prednisolone and oral ginkgo biloba (control) or oral prednisolone and oral ginkgo biloba in combination with intratympanic dexamethasone.

Recovery of the PTA threshold at 2, 4, and 8 kHz was statistically significantly related to both the initial hearing loss and the method of treatment. Interaction effects revealed greater recovery in those who had greater initial hearing loss regardless of treatment, as well as an overall increase in recovery in the group that received the additional intratympanic treatment. Across participants, recovery of function ranged from $\sim$10 to $\sim$50 dB, with 10–20 dB recovery in those with 30–40 dB HL PTA thresholds at study entry, and 20–50 dB recovery in those with 60–70 dB HL PTA thresholds at study entry.

The only completed nonmilitary study was a Phase 1/2 double-blind, randomized, parallel-dose design enrolling participants after firecracker exposure on New Year's Eve (173). Pretreatment thresholds were measured within 24 h of the noise exposure, and intratympanic AM-111 administered if the 4 and/or 6 kHz thresholds were $\sim$30 dB HL. Three days post-treatment, the average threshold improvement (PTA at 4 and 6 kHz) was 11 ± 14 dB, and 30 days later the average

improvement was 14 ± 16 dB, although an untreated or placebo-treated group against which recovery could be compared was not included.

From the published data table [see table 1 in Suckfuell *et al.* (173)], it is possible to calculate that the average threshold recovery in the lower dose group was 9 ± 10 dB at 3 days and 7 ± 6 dB at 30 days ($n = 7$ participants). For the smaller group ($n = 4$) receiving the higher dose, threshold recovery was 16 ± 16 dB at 3 days and 20 ± 20 dB at 30 days. Thus, significant variability in the recovery across participants was observed within each dose group.

Two additional clinical trials evaluating the potential for otoprotection using drugs administered subsequent to noise exposure are not yet recruiting. In NCT04768569 (138), a subset of the patients will be randomized to a postnoise rescue condition, with placebo administered before skull-based surgery and active treatment administered subsequent to skull-based surgery. The control group will receive placebo both before and after skull-based surgery. In NCT04774250 (139), safety officers will be screened for TTS of ≥ 10 dB at 3, 4, or 6 kHz immediately after weapons training/weapons testing. Those that have a documented shift will be randomized for postnoise rescue treatment. Inclusion of baseline testing and control groups in the not yet recruiting studies increases study rigor relative to completed studies described in Table 2.

PTS prevention (pretreatment) versus PTS rescue (post-treatment)

It is difficult to compare outcomes across studies given the variety of reporting metrics. Studies evaluating the efficacy of pretreatment regimens have compared prenoise (baseline) hearing with postnoise audiometric hearing to determine the degree of hearing loss that developed as a consequence of a common loud event, with the three completed studies evaluating outcomes in three different military populations required to participate in three different weapons training events using three different primary audiometric outcomes. The rate at which STS developed varied from as low as 2% to as high as 53%, depending on the specific definition of STS and the study population, with the greatest rate of STS generally being observed for STS defined as a change in hearing ≥ 15 dB at one or more frequencies in at least one ear.

In studies investigating postnoise rescue, prenoise baselines were not available, and instead of tracking the rate or degree of noise-induced deficits, the initial postnoise (injured) threshold was used as a baseline against which drug-mediated recovery was measured, with interpretation of recovery complicated by the lack of untreated or placebo control groups. Collapsed across doses, Suckfuell *et al.* (173) reported some 10–15 dB of recovery at 4 and 6 kHz, whereas Zhou *et al.* (197) reported an increase in the rate at which threshold recovery ≥ 15 dB at 2, 4, and 6 kHz or word recognition score recovery $\geq 15\%$ occurred (with 23%–52% of the two groups meeting these criteria). Chang *et al.* (27) did not report average recovery or rate of recovery, but rather the statistical interactions between treatment and pretreatment threshold, with individual recovery ranging from ~ 10 to 50 dB for the average of 2, 4, and 8 kHz.

Across these six completed studies, five of which included soldiers exposed to weapons fire, the primary outcomes have varied from study to study, and the rate and degree of noise

injury in the control conditions have varied, with none of the postnoise rescue studies including an untreated or placebo-treated control condition. The two clinical trials that are not yet recruiting [NCT04768569 (138), NCT04774250 (139)] include different populations (patients exposed to skull-based surgical drilling noise, safety officers engaged in weapons training/weapons testing), and the primary outcome will be the rate of PTS ≥ 10 dB at 2, 3, 4, or 6 kHz 30 days postnoise, with the rate of NIOSH STS being reported as a secondary outcome.

TTS prevention: laboratory and real-world designs

A larger number of clinical trials have evaluated prevention of TTS using pretreatment approaches (Table 3) compared with post-treatment approaches (Table 4). Some of these studies have used military weapons training models. For example, several studies investigating prevention of TTS after weapons training have been conducted in partnership with the Swedish Armed Forces, using either pretreatment [see Table 3, Le Prell *et al.* (104)] or post-treatment [see Table 4, Lindblad *et al.* (114)] interventions. However, these studies have largely failed to measure significant amounts or rates of TTS in either treated or placebo (control) conditions. Consistent with the above discussion of lower than expected rates of PTS, the smaller than expected rates of TTS may reflect more careful use of HPDs by participants enrolled in clinical trials evaluating noise-induced changes in hearing.

Similarly small and variable TTS deficits were reported for clinical trials enrolling participants exposed to nightclub noise in Toppila *et al.* (182) and Kramer *et al.* (85). In the Finnish study conducted out of Tampere University, exposures were 93 dBA for 4 h, and TTS was 7–9 dB at 4 kHz when measured 2 min postmusic. Sound exposures were more variable in the U.S. nightclub study conducted by Kramer *et al.* (85) with the 2-h L_{avg} sound exposure levels ranging from 92.5 to 102.8 across eight subgroups. The average TTS at 4 kHz was 14 dB when measured 5 min postexposure and 9 dB when measured 20 min postexposure, but significant variability was observed across participants, presumably at least in part as a consequence of the different exposure levels from group to group.

Comparisons of TTS and its prevention are also difficult for studies conducted in loud workplace settings, such as NCT00552786 [for complete report, see Lin *et al.* (112)], Doosti *et al.* (34), and Kapoor *et al.* (74). Kapoor *et al.* (74) documented 4–6 dB postshift TTS from 2 to 8 kHz in Indian Army Base workers exposed to 98.3–108.1 dBA noise for 5 h without HPD. Postshift TTS as reported by Lin *et al.* (112) and Doosti *et al.* (34) was smaller. Lin *et al.* (112) documented an average of 2.8 dB postshift TTS for the frequencies of 3, 4, and 6 kHz in steel industry workers in Taiwan exposed to 88–89 dBA noise for 8 h without HPD. Doosti *et al.* (34) documented average changes of 2–3 dB postshift at each of the test frequencies (4, 6, and 16 kHz) in textile industry workers in Iran exposed to >85 dBA noise for 8 h without HPD. Statistically significant decreases in TTS were reported for all three clinical trials, but the clinical significance of these reductions is not clear when the average TTS was <5 dB in each study.

Data from laboratory studies have been more successful in demonstrating the potential for TTS prevention with larger

and more clinically relevant TTS induced in some, but not all, study designs. Laboratory-based TTS prevention studies contrast with the PTS prevention studies, in that they have primarily used steady noise rather than impulse noise.

Two early studies utilized a 1 kHz pure tone at 100 dB SPL for 10 min (69, 194). In both studies, TTS in control conditions ranged from ∼20–25 dB at 2 min postexposure to ∼5 dB at 1 h postexposure, with no remaining shift the following day. Also employing a pure tone, but using a 3 kHz tone at 90 dB HL for 10 min, were the recent investigations by Quaranta *et al.* (160) and Staffa *et al.* (170). In both studies, threshold shift in control conditions was significant at 2 min postexposure (4 kHz: 10–20 dB; 6 kHz: 16–30 dB) with significant recovery within 15 min and thresholds fully recovering within 1 h, although tinnitus was reported for 24 h.

Narrowband noise centered at 3 kHz has been presented at 112-dB SPL for 10 min (159); 2 min postexposure, mean TTS in control conditions was 2.9 dB at 1 kHz, 5.2 dB at 2 kHz, 16.6 dB at 3 kHz, and 21.5 dB at 4 kHz. Other laboratory investigations have used exposure to white noise, with paradigms including presentation at 100 dBA for 20 min (28), 90 dB SL for 10 min (6), and 90 dB HL for 15 min (37). While Fetoni *et al.* (37) reported DPOAE amplitude reductions, but no TTS, with 90 dB HL white noise for 15 min; Attias *et al.* (6) reported DPOAE threshold shifts were ∼5–7 dB from 2 to 6 kHz, and 28% of ears had TTS ≥20 dB at 2 min postexposure with 90 dB SL white noise for 10 min. The largest TTS 2 min postexposure in any participant was 40 dB, and mean TTS was 10–15 dB at 3 kHz and 15–20 dB at 4, 6, and 8 kHz (6). Noise-induced TTS 2 min after 20-min exposure to 100-dBA white noise as reported by Chaturvedi *et al.* (28) was consistent with that reported by Attias *et al.* (6).

Although these laboratory studies yield a high degree of stimulus control, the signals are not reflective of common real-world experience, prompting the development of a laboratory-based calibrated music exposure model (100, 108). Calibrated PAS music exposures have been delivered (or were planned to be delivered) in NCT01444846 (130) [see complete report in Kil *et al.* (78)], NCT00808470 (129) [see complete report in Le Prell *et al.* (101)], NCT02257983 (132) (completed, results not posted), and NCT02049073 (131) (withdrawn). In these clinical trials, music was delivered (or was planned to be delivered) at sound levels of ∼100 dBA for 4 h, with sound level calibrated in an artificial ear coupler to mimic the sound levels expected in the average ear canal. Converting this coupler-based measurement to a free-field equivalent level using a conservative 5-dB transfer function of the open ear (TFOE), the exposure is equivalent to 95 dBA. Thus, the calibrated 4-h exposure would provide 100% of the OSHA permissible exposure limit (PEL) [for discussion, see Le Prell *et al.* (100)].

Recent data from children, adolescents, and adults revealed TFOE measurements ranging from 5 to 20 dB with an average of 10 dB (43, 44). If a study participant had the average adult TFOE of 10 dB, the free-field equivalent exposure level for that individual would be 90 dBA, and their 4-h dose would then be 50% of the OSHA PEL. If a study participant had a larger than average TFOE of 20 dB, the free-field equivalent exposure level would be 80 dBA, and the 4-h dose would then be 12.5% of the OSHA PEL for that individual, a significant contrast to a participant with a 5-dB TFOE expected to receive 100% of their daily noise dose after adjusting for the 5-dB TFOE.

Although TFOE was not measured in the clinical trials listed above, TTS measured in the individual participants' 15 min postexposure ranged from 0 to ∼20–25 dB at the most affected 4 kHz frequency. Average TTS in the three different cohorts of untreated and placebo group participants ranged from 4 to 6 dB across studies (78, 100, 101). The large individual differences in TTS despite the controlled laboratory-based in-ear exposure highlight the possibility that TFOE, or other sources of individual variability, importantly influence TTS. Direct measurement of the potential for confounding effects of TFOE on TTS and PTS is warranted to determine if this factor needs to be controlled in future clinical trials.

The observed reductions in average TTS were statistically significant in NCT01444846 (130), and the detailed report by Kil *et al.* (78) also included a secondary analysis in which decreases in the prevalence of ≥10 dB TTS at any tested frequency were shown. Decreases in the rate of STS will be the primary outcome measure used in NCT02779192 (133), with hearing-in-noise tests providing a secondary outcome. The selection of threshold shift ≥10 dB as a primary outcome is supported by the guidance in Campbell *et al.* (19), which states, ''a reduction in the incidence of a ≥10 dB threshold shift would be considered significant and clinically relevant, since a 10-dB loss in hearing sensitivity requires a 10-fold increase in sound intensity to evoke an accurate behavioral response using pure-tone audiometry.''

Clinical trial endpoint selection: threshold shift ≥10 dB

It is encouraging that many of the studies listed in Tables 1–4 provided evidence of reliable reduction in human NIHL, suggesting that study drugs reached the inner ear and were bioactive. Nonetheless, the majority of studies enrolled participant populations in which significant PTS (*i.e.*, meeting study-specific STS criteria) developed in a small subset of participants (Tables 1 and 2) or in which the average TTS was small (*i.e.*, <10 dB) (Tables 3 and 4). As noted above, Kil *et al.* (78) dealt with this issue by defining ≥10 dB threshold shift as a primary endpoint, a strategy that was advocated in Campbell *et al.* (19), and several upcoming (not yet recruiting) studies are following the same strategy.

As part of the rationale for a criterion of ≥10 dB threshold shift as a study outcome, Campbell *et al.* (19) suggested that a 10-dB improvement in hearing sensitivity would potentially allow for better word recognition, especially in environments with background noise and a low (≤6 dB) SNR. The remainder of this section discusses use of that 10-dB shift criterion for frequencies through 8 kHz. In the EHF range (>8 kHz), test–retest reliability is poorer, and threshold shifts of 10 dB at a single frequency cannot be distinguished from test–retest variation.

The definition of STS as ≥10-dB threshold shift at one or more frequencies (through 8 kHz) as a clinical trial endpoint is likely to be controversial as it provides an endpoint that is less conservative than the STS definitions adopted for regulatory use by federal agencies (OSHA, NIOSH, Mining Safety and Health Administration [MSHA], DoD). Nonetheless, the use of this measure as a primary or secondary clinical trial endpoint warrants consideration. First and foremost, the regulations enforced by OSHA are a political compromise, promulgated after significant public comment and lobbying by industry (175).

Well before an STS is documented (*i.e.*, ≥10-dB average hearing loss at 2, 3, and 4 kHz), significant DPOAE shifts occur, suggesting that noise-induced OHC loss or dysfunction is evident in advance of STS meeting the OSHA (1983) criteria. By the time an OSHA STS is documented, significant hearing loss at the higher frequencies (including not only 6 and 8 kHz but also the EHF frequencies) is likely. In addition, hearing-in-noise deficits can be observed even if there is no STS (*e.g.*, 111, 152). In other words, cochlear injury, including injuries that compromise hearing-in-noise function, occurs well in advance of OSHA-defined STS criteria, and prevention of such injuries has the potential to be clinically significant.

The definition of STS as ≥10-dB threshold shift at one or more frequencies (through 8 kHz) as a clinical trial endpoint is also less conservative than the STS definitions adopted by audiology credentialing bodies that have published criteria for identification of significant ototoxic injuries (ASHA, AAA). Drug-induced hearing loss is highly probable during the administration of drugs such as cisplatin and the aminoglycoside antibiotics, with hearing loss well known to begin in the EHF range and progressively extend to lower frequencies, including frequencies important for speech perception [for review, see Campbell and Le Prell (20)].

Given the high probability that frequencies important for speech will eventually be affected, ototoxicity monitoring has two purposes. The first purpose is to prompt the consideration of a less toxic drug regimen by the prescribing physician to prevent progression of hearing loss. The second purpose is to prompt audiological rehabilitation efforts with listening devices or hearing aids as needed, to assure patients can communicate effectively when they do develop drug-induced changes in their hearing (3, 5).

The decision to alter life-saving cisplatin or aminoglycoside antibiotic drug therapies is balanced against the risk of handicapping hearing loss; interviews with oncologists and pulmonologists reveal concerns over both hearing loss and limited alternative treatment options when hearing loss does develop (38). However, ameliorating noise injury does not require this balancing act.

It is now well known that DPOAEs and EHF thresholds are more sensitive for monitoring ototoxicity than the conventional speech frequency audiogram, and discussion of improving ototoxicity monitoring using these more sensitive DPOAE and EHF tools is available (80, 116), although limitations of these tools have also been noted (151). DPOAEs and EHF testing were notably not widely available at the time the ASHA (1994) criteria were developed, and even at the time of development of the AAA (2009) criteria, concerns about the lack of standardization for EHF testing and inability to measure DPOAEs elicited by tones outside of the conventional frequency range (through 8 kHz) remained.

Taken together, the pattern of hearing loss observed across the body of studies listed in Tables 1–4 clearly establishes that the rate of observed STS varies based on both the exposure and the definition of STS. In addition, the data show that the rate of STS can be relatively high even when the average change at any single frequency is small. As an example, frequency-specific average threshold shift was ≤1.0 dB from 1 to 20 kHz in right, left, and both ears in the placebo group described by Kopke *et al.* (83), whereas STS rates ranged from 12% to 53% across the various subgroups and

definitions of STS. Similarly in Kil *et al.* (78), frequency-specific average threshold shift ranged from ~2–4 dB from 0.25 to 8 kHz in the placebo group, whereas STS rates were ~60% (using the definition of STS as threshold shift ≥10 dB).

Questions might be raised regarding the interpretation that ≥10 dB shifts observed by Kil *et al.* (78) were "real" noise-induced shifts, given that the criterion was more liberal than criteria used by OSHA, NIOSH, and others. However, treated participants had both smaller average TTS and a reduced rate at which 10 dB shifts were observed, and the percentage of participants with ≥10 dB shifts systematically decreased with time postexposure, with only ~5% of participants meeting the STS criteria 24 h later.

If test–retest is a concern when using the criteria of deficits ≥10 dB, one of the strategies discussed by Dobie (32) could be considered. Dobie (32) suggested the potential for improvements in the accuracy of estimates of the rate of STS, given test–retest uncertainties that could be accomplished by subtracting the rate at which threshold improvements ≥10 dB are observed from the rate at which threshold deficits ≥10 dB are observed. The rate at which threshold improvements were observed was not reported by Kopke *et al.* (83), Kil *et al.* (78), or other papers listed in Tables 1–4, but this strategy could increase confidence that reported STS rates reflect real effects of noise and not test–retest uncertainties that can occur even in the absence of noise exposure.

Confidence that threshold shifts are real effects of noise is critical within clinical trials on NIHL prevention. At an individual level, small threshold shifts cannot be distinguished from test–retest reliability. Early work by Brown (17) showed a high degree of correlation across threshold measurements for participants retested using the same equipment (correlation coefficient = 0.95), with test-to-test differences averaging −0.34 dB (since thresholds at the second test can be either better than or poorer than at the first test, average differences should be near 0) and a standard deviation of 6.1 dB.

Comprehensive discussion of the issue of test–retest reliability was provided by Dobie (32), who notes that only 7% of threshold shifts would be ≥10 dB and <1% of threshold shifts would be ≥15 dB by chance alone, assuming that a 5-dB step size is used during testing and that the standard deviation of the test-retest difference scores (SDdiff) is 5 dB. If SDdiff increases to 10 dB (*i.e.*, greater variability from test to test in the absence of other factors such as noise exposure), then 11% of threshold shifts would be ≥15 dB by chance alone, highlighting the importance of verifying the reliability of threshold measurements for each participant.

The detailed literature review by Dobie (32) provides a number of examples of real-world data sets in which SDdiff has been 3–4 dB for frequencies up to 4 kHz and 5–8 dB at 6 and 8 kHz, with SDdiff increasing as the amount of time between tests increases. If a liberal criterion, such as threshold shift ≥10 dB at one or more frequencies, is adopted for use in clinical trials, the rate at which threshold improvements ≥10 dB are observed should be monitored and reported to investigate the possibility of random variability underlying the observed changes. The suggestion by Dobie (32), to subtract the rate at which threshold improvements of ≥10-dB are observed from the rate at which threshold deficits ≥10-dB are observed, warrants discussion and consideration.

OAEs as clinical trial outcomes

As introduced above, OHCs are highly vulnerable to noise injury, significant OHC loss can accrue before measurable audiometric threshold shift, and DPOAEs have been proposed as monitoring tools both in industrial hearing conservation and in clinical trials (81, 82). Review of the NIHL clinical trial literature revealed DPOAEs to be used more commonly than TEOAEs, and DPOAEs to be more commonly included as secondary outcomes than as primary outcomes. Recommendations for inclusion of DPOAEs in studies on human noise injury have been highlighted in recent years, given interest in the earliest effects of noise on the inner ear (15, 93).

Despite the above strengths, there are also reasons for caution in the use of DPOAEs as clinical trial outcomes. As discussed in Campbell and Le Prell (20), OAEs can be compromised by otitis media, cerumen, and particularly in the case of blast-induced NIHL, tympanic membrane perforation. Thus, if OAEs are to be used to document noise injury, documenting the integrity of middle ear sound transmission is important.

A more challenging issue is that no professional consensus documents or widely accepted standards for OAE data collection and analysis exist, which results in variable methodologies across studies and makes repeatability from study to study uncertain. Perhaps most importantly, criteria for what constitutes a clinically significant OAE change are not available, and it is unclear how OAE changes in a longitudinal study will correlate with clinically impactful changes in human communication ability.

Kopke *et al.* (83) reported some changes in DPOAEs, but those changes were not correlated with observed pure-tone threshold changes. Outside of the clinical trial literature, however, Parker (152) reported statistically significant correlations between DPOAE amplitude and hearing-in-noise ability. Thus, DPOAEs do remain of interest as a possible biomarker for cochlear injury that is independent of attention, cognition, and language ability. A final cautionary note is that OAEs are specific to OHC function, and even if an otoprotective agent prevents changes in OAEs, noise-induced damage to other structures (*e.g.*, damage to the stria vascularis, cochlear synaptopathy, damage to the central auditory pathways) could affect hearing ability in the absence of changes in OAE metrics.

Despite the above caveats, use of OAE outcomes should be considered within clinical trials on NIHL otoprotection as they provide an important biomarker for OHC protection, even if they do not ultimately correlate with other functional tests. Given imperfect relationships between OAE measures and hearing sensitivity, and uncertain functional significance of changes in DPOAE amplitude that precede threshold shift, it currently appears to be more appropriate for DPOAEs to continue to serve as secondary or other outcomes [for additional discussion, see Le Prell and Campbell (98) and Le Prell and Lobarinas (105)].

EHF audiometry as clinical trial outcomes

As introduced above, a variety of recent research studies investigating the earliest effects of noise injury noted EHF threshold deficits in the absence of hearing loss ≤8 kHz, suggesting that EHF audiometry may be more sensitive to noise injury than threshold tests at frequencies through 8 kHz. EHF audiometry is similarly well documented as extremely useful for ototoxicity monitoring. Ototoxic drugs such as aminoglycoside antibiotics and cisplatin almost invariably affect the basal cochlea first with hearing loss observed first in the EHF range, and then progressing in a relatively systematic manner into the lower conventional frequency range.

While the loss of hearing in the EHF range is not established as clinically impactful for most humans, changes in EHF audiometry with ototoxic medications clearly predict impending changes in the conventional frequency range that *will* have clinically significant impact on communicative function. A similar pattern of progression has not been consistently documented for NIHL; that is, we do not yet have longitudinal studies showing that EHF hearing loss in noise-exposed individuals is predictive for later development of hearing loss in the notch area, between 2 and 6 kHz. In the absence of longitudinal data, it is not clear if EHF testing in individuals exposed to noise will have the same value as EHF testing for drug-induced hearing loss. Longitudinal studies investigating progression of hearing loss from EHF to lower (''notch'') frequencies are needed.

Despite the above limitations, EHF hearing is considered particularly important for musicians and other performing artists (191), with monitoring of EHF thresholds recommended for monitoring hearing loss in these populations (4). Thus, even though the inclusion of this metric has not been common in studies to date, clinical trials that selectively recruit participants who rely on EHF thresholds should consider measuring EHF thresholds as a secondary or other outcome as previously discussed by others (15, 93, 98, 105). For the vast majority of populations that do not explicitly rely on EHF hearing, EHF testing can be considered as a potential secondary outcome, but the clinical significance of inferred damage to the basal cochlea will need to be carefully considered. In addition, age-appropriate norms will need to be used (162, 171).

Despite the above caveats, it should be noted that EHF thresholds are increasingly recognized as important for hearing in noise (126). If the health of the basal cochlea and corresponding EHF hearing is important for hearing in noise, this could prompt greater interest in using this additional outcome measure to document possible protection of the basal cochlea against noise injury.

Speech and speech-in-noise tests as clinical trial outcomes

Tables 1–4 reveal that inclusion of speech or speech-in-noise tests as primary or secondary endpoints in NIHL otoprotection trials is not common. The lack of speech and speech-in-noise tests as primary or secondary endpoints is noteworthy, given that the American Academy of Otolaryngology (AAO) recommends word recognition performance be included in all clinical trials that assess auditory function, and that presentation of these word recognition data be considered the minimum publishing requirement (49). The Gurgel *et al.* (49) guidelines require that word recognition scores (percentage correct) and the PTA at 0.5, 1, 2, and 3 kHz be provided in a scatterplot, so that relationships between hearing loss and word recognition deficits are clearly shown.

The Gurgel *et al.* (49) guidelines raised concern in the audiology community as evidenced by a letter to the editor from the President of the AAA (24). One of the concerns was that word recognition testing can be problematic for clinical trials that include subjects with English as a second language or in clinical trials extending across many countries with different primary languages. Another concern was that the PTA at 0.5, 1, 2, and 3 kHz is not particularly informative for ototoxicity monitoring or for measurement of NIHL. In their response to Dr. Carlson's letter, Jackler *et al.* (65) encouraged that additional data be provided when the minimal (standardized) data are not sufficient, word recognition scores be omitted for young children and populations in which word recognition scores are not routinely collected, and the standard not be followed when it is not applicable to the study population.

Based on the Gurgel *et al.* (49) guidelines, it may be worthwhile to include word recognition scores in clinical trials on NIHL prevention. However, the available data suggest that speech-in-noise or hearing-in-noise tests are probably even more important to consider including within the study design. The lack of inclusion of speech in noise in studies evaluating otoprotection is particularly notable, given that difficulty understanding speech in noisy environments is the most commonly hypothesized functional effect of noise-induced neuropathic damage [(87, 93, 99, 113, 118, 154), see also the detailed discussions by Plack *et al.* (155, 156)]. However, OHC damage is also associated with speech-in-noise deficits [see, *e.g.*, Hoben *et al.* (62), Leger *et al.* (110), Parker (152), Summers *et al.* (174)].

Because noise can damage both OHCs and neural pathways, hearing-in-noise tests are likely to provide a compelling functional outcome in clinical trials. Speech-in-noise (and other hearing-in-noise) tests can be supplemented by DPOAEs as an additional quantitative measurement of OHC function to aid in interpretation of drug-mediated benefits.

As noted above, Campbell *et al.* (19) suggested that a 10-dB improvement in hearing sensitivity would potentially allow for better word recognition, especially in difficult (noisy) listening environments. The review by Le Prell and Clavier (99) provides detailed discussion of multiple studies in which hearing-in-noise deficits were measured in noise-exposed study participants even though threshold sensitivity was within 5–10 dB relative to unexposed controls (*i.e.*, 2, 63, 86, 90, 111, 172).

Since then, Grinn *et al.* (45) documented clinically significant changes in the Words-in-Noise (WIN) test 1 day after recreational sound exposure even in the absence of measurable TTS. Word-in-noise deficits grew as the recreational exposure grew, with the most notable deficits detected when recreational activities accrued a cumulative noise dose exceeding the OSHA permissible daily exposure (90 dBA time-weighted-average).

Relationships between recreational sound exposure and hearing in noise ability were not replicated by Wang *et al.* (190), however, who used the Mandarin Hearing-in-Noise test 1 day after music festival attendance. Additional research is warranted to understand both noise-induced hearing-in-noise deficits and prevention of this dysfunction. Monitoring EHF threshold and DPOAE amplitude in combination with hearing in noise would potentially provide insight not only into potential otopathologies suggested to be associated with threshold shifts but also those associated with hearing-in-noise deficits that occur in the absence of either TTS or PTS.

A variety of hearing-in-noise tests could be considered for inclusion in clinical trials evaluating drugs for otoprotection purposes. The multitude of available tests include the Quick Speech-in-Noise test (QuickSin) (79), WIN test (193), Hearing-in-Noise Test (HINT), Bamford-Kowal-Bench Speech-in-Noise Test (BKB-SIN) (35), various digits-in-noise tests (184), and custom tests with reverberation and/or time compression added (111). The potential inclusion of hearing-in-noise tests in clinical trials has been discussed in detail elsewhere (93, 97–99). Advocacy of a specific test is outside the scope of this review. However, the urgency of this issue is clear when considering the need for documentation of functional benefit in pivotal Phase 3 trials and the importance of this functional measure in affected patients. If included, language issues must be considered, as participants do more poorly on hearing-in-noise tests when they are not delivered in their native language.

Electrocochleography metrics as clinical trial outcomes

Electrocochleography was only rarely noted in Tables 1–4. If the search criteria are expanded beyond NIHL prevention, however, a few studies incorporating ABR measures in addition to the audiogram can be found in trials recruiting populations with existing sensorineural hearing loss and/or speech-in-noise difficulties [see, *e.g.*, NCT04462198 (137); NCT04129775 (136); for review, see 95].

There has been significant exploration of different electrophysiological measures that may be sensitive to cochlear synaptic pathology, including ABR Wave 1, the envelope following response, the frequency following response, and the middle ear muscle reflex [for review, see Bramhall *et al.* (15)]. Test–retest reliability data have been provided for many of these tests (47, 73, 158). Bharadwaj *et al.* (14) importantly discuss high test–retest reliability not necessarily being sufficient given individual differences in cochlear mechanical dispersion, EHF threshold deficits, anatomical factors, *etc.*, noting that any diagnostic test for cochlear synaptopathy must capture "individual variations in synaptopathy over and beyond the variance that is imposed by the host of extraneous factors."

Interest in new diagnostic tools with increased sensitivity for the identification of specific otopathologies is likely to remain high (152), particularly in the context of investigational medicines that might repair synapses damaged by noise exposure and/or aging (176, 189). Taken together, the clinical significance of changes in evoked potentials requires additional investigation, as discussed in recent review papers (*e.g.*, 14, 15, 93) and as discussed above for OAEs. Given this, electrophysiological measures are likely to remain more appropriate for use as secondary or other outcomes in most clinical investigations.

Despite the above caveats, electrocochleography is and will remain particularly important in the monitoring of neonates and children receiving ototoxic drug interventions (16, 39). There is significant concern about sound levels in neonatal intensive care units (NICUs) exceeding limits (21, 168), associations between NICU care and hearing loss (12), and interventions are beginning to be investigated (1, 11). If

infants or children were included in future otoprotection studies, the use of evoked potentials as a primary outcome would likely be necessary.

Tinnitus measures in clinical trials

As summarized in Table 5, questions about tinnitus were included as a secondary outcome in 8 of 31 clinical trials (26%), and only one clinical trial used a validated survey (the THI, as discussed above). Tinnitus is a well-known side-effect of many medicines and should be monitored (31). In addition, tinnitus is highly relevant to include in studies on the prevention of NIHL as it is a common comorbidity of NIHL as well as other forms of acquired hearing loss, such as ototoxic drug-induced hearing loss. An unanticipated increase in the rate of temporary music-induced tinnitus was reported for NCT00808470 (129) [for complete report, see Le Prell *et al.* (101)], suggesting the possibility that some drugs may interact with noise, with tinnitus emerging during conditions of noise-induced cochlear stress and not simply as a function of drug treatment.

Use of tinnitus surveys in clinical trials evaluating prevention or amelioration of tinnitus (50, 58, 59) and the use of tinnitus surveys in ototoxicity monitoring (20) have been extensively discussed. A few of the better known tinnitus surveys, in roughly chronologic order of development, are the Tinnitus Questionnaire (TQ) (10, 52), Tinnitus Handicap Questionnaire (THQ) (89, 145), Tinnitus Reaction Questionnaire (TRQ) (192), THI (8, 141), Tinnitus Ototoxicity Monitoring Interview (TOMI) (36, 101, 104), and the Tinnitus Functional Index (TFI) (119), but this is by no means a comprehensive list.

As noted above, a recent systematic review found 33 tinnitus questionnaires described in the literature (187). Although Kamalski *et al.* (72) found that the TQ, THI, TRQ, and THQ were among the most used surveys, their systematic review was conducted before the publication of the TFI. The TFI has been used in several tinnitus clinical trials (13, 60, 180), and it has been used in studies on noise-induced tinnitus (66). Greater consistency in measurement and reporting of tinnitus within studies on NIHL prevention is urgently needed, and updated review of the literature would be helpful in guiding the selection of tinnitus measurement tools.

Until there is evidence that can guide the selection of tinnitus metrics that are the most appropriate for noise-induced tinnitus treatment and/or prevention of noise-induced tinnitus, the guidance of Newman *et al.* (142) should be considered. They provide an important discussion of not just the issue of test–retest reliability, but also the importance of measurement error and confidence intervals in determining whether a true change has occurred on a questionnaire. In their discussion, Newman *et al.* (142) point to advantages of open-ended questions, in that patients are not limited to fixed response options, but also disadvantages of open-ended questions in that responses are difficult to quantify both across time and across patients.

Patient-reported outcome measures

As noted in the results, no hearing-specific PROMs were reported in any of the investigations summarized in Tables 1–4, although a few studies included questions or ratings regarding tinnitus annoyance or tinnitus bothersomeness. With respect to patient-reported tinnitus outcomes, Newman *et al.* (142) advocated use of the patient global impression of change score. This is documented using a single question that asks the patient to indicate the amount of change from ''much better'' through ''no change.''

While such questions are highly relevant to treatment-related alleviation of current symptoms, a major obvious challenge with prevention research is that ''no change'' is the desired treatment outcome, and the control group must report negative outcomes for preventive benefits to be documented. The identification of study populations in which significant negative outcomes are expected has been a challenge. It seems likely that participants in real-world studies used required HPDs more consistently and/or more correctly during study enrollment, given that the rate of hearing loss in control participants was less than expected in several completed investigations using both TTS and PTS models.

Occupational safety regulations require the provision of effective hearing conservation programs, and it is not ethical to compromise hearing conservation program standards. Thus, workplace studies have important considerations.

Feasibility of studies on the prevention of PTS due to occupational noise

The major issue of NIHL for noise-exposed workers was recently described by Themann and Masterson (179), with the resulting conclusion that little progress has been made with respect to noise exposure and occupational hearing loss within many industry sectors. They note the major issue of suprathreshold deficits that compromise quality of life before the development of a hearing loss meeting OSHA STS criteria.

OSHA-enforced hearing conservation programs defined in 29 CFR 1910.95 are intended to protect workers with an identified risk of auditory injury. Audiometric monitoring is completed once per year to determine if significant change in hearing has developed. In other words, the effects of an entire year of exposure are captured during a single hearing test, and the tests are repeated annually over many years to identify slow, progressive changes in hearing.

Given the large numbers of affected workers, and the mandated annual testing, the development of new relationships with corporate entities to allow the recruiting of noise-exposed workers into clinical studies is appealing. However, a major challenge for any clinical trial will be the potentially relatively small subset of worker (and other) populations that will develop an OSHA STS; across industries, the incidence of new (not previously measured) material hearing loss ranges from 4% to 10% (179). The inability to predict which workers will be the most vulnerable to NIHL and should be recruited into the clinical trial is a major challenge, with very large numbers of participants needed to obtain adequate study power.

Recently, Le Prell *et al.* (102) discussed various threshold shift criteria that might be considered for use in clinical trials, including the rate at which PTA thresholds at 0.5, 1, 2, and 3 kHz (PTA5123) exceed 25 dB HL (the definition used by the AAO-HNS to specify where impairment begins), or, the rate at which PTA thresholds at 1, 2, 3, and 4 kHz (PTA1234) exceed 25 dB HL (the definition used by ASHA to specify where impairment begins). The rate of changes of ≥10 dB in
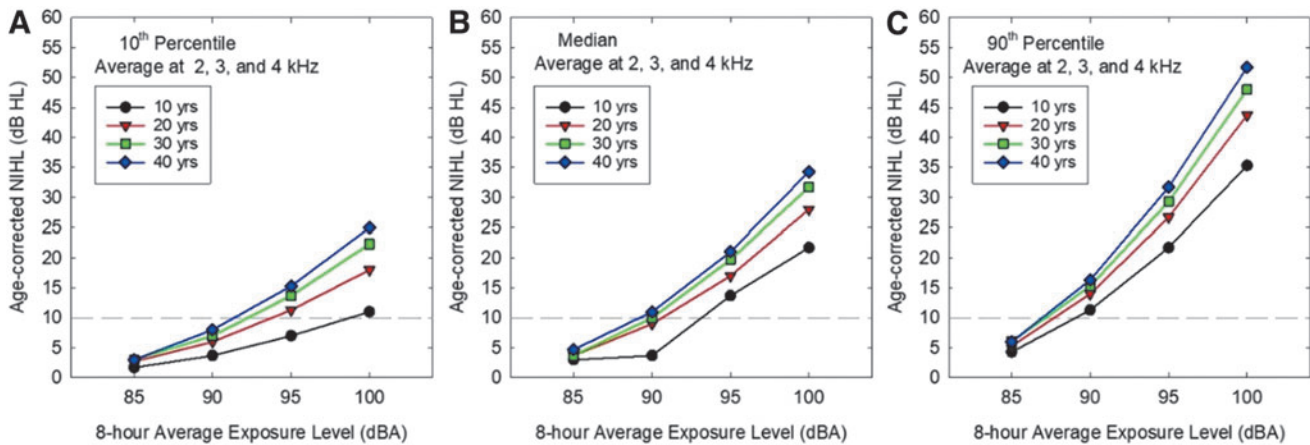
FIG. 1. ISO-1999 data for 2, 3, and 4 kHz NIHL averaged together to determine the exposure conditions in which OSHA STS would be expected based on ISO-1999 data for the 10th (A), 50th (B), and 90th (C) percentiles for workers exposed to different sound levels (85, 90, 95, or 100 dBA) over different career durations (10 years: *black circles*; 20 years: *red triangles*; 30 years: *green squares*; 40 years: *blue diamonds*). Data shown here are the average effects of noise at 2, 3, and 4 kHz after subtracting the median age-related hearing loss, with the *dashed line* marking a 10-dB average threshold shift, which is defined as an OSHA STS. NIHL, noise-induced hearing loss; OSHA, Occupational Safety and Health Administration; STS, significant threshold shift.

the PTA threshold at 2, 3, and 4 kHz could be assessed (the definition used by OSHA for STS), or the rate of changes of ≥15 dB at a single frequency could be assessed (the definition used by NIOSH for STS).

A major challenge discussed in that report is the low rate at which such injuries would be expected based on large epidemiological data sets (64, 148). To illustrate the challenges of adopting OSHA STS as an endpoint in a clinical trial, the data tables in ISO-1999 were used to calculate expected NIHL at the 10th, 50th, and 90th percentiles for workers exposed to different sound levels (85, 90, 95, and 100 dBA) over different career durations (10, 20, 30, and 40 years) after subtracting out the expected effects of aging (which is necessary because the expected effects of aging have the potential to confound estimates of hearing loss due to noise exposure). From these frequency-specific data, the expected noise-induced threshold shift was calculated for the average change at 2, 3, and 4 kHz. Predicted hearing shift at 2, 3, and 4 kHz is plotted in Figure 1.

As seen in Figure 1C, the 85-dBA TWA exposures are not expected to result in OSHA STS even in the most vulnerable 10th percentile after 40 years of work exposure. At 90-dBA TWA, the upper allowable exposure, the median population shows an OSHA STS shift after 20 years (Fig. 1B), with the most vulnerable 10th percentile meeting the 10-dB shift criteria at 10 years of exposure (Fig. 1C). At 95 and 100 dBA exposures, which exceed the PEL, STS is anticipated for the median worker within 10 years (Fig. 1B), and even the least vulnerable 10th percentile will develop an OSHA STS within 10–20 years (Fig. 1A). However, for both ethical and regulatory compliance reasons, it would not be permissible to run a drug study enrolling workers with 95 or 100 dBA daily exposure unless they wore HPDs to reduce their exposure, so that it does not exceed the PEL.

HPDs will reduce exposure for different workers by different amounts, given that HPD use varies across employees. Obviously, if different frequencies are included in the PTA, the rate at which hearing loss is expected to develop will

change, with more hearing loss measured if the frequencies of 3, 4, and 6 kHz are considered, and less hearing loss if the frequencies of 0.5, 1, and 2 kHz are considered [for detailed discussion and illustration of PTAs using other frequency combinations, see Le Prell *et al.* (102)]. Other data sets used by OSHA during the development of the hearing conservation amendment are also available (148) with similar resulting conclusions despite the difference in data sets (96).

Taken together, the data plotted in Figure 1 suggest that studies evaluating prevention of workplace STS would have to monitor participants working in high noise environments for multiyear durations to assure that STS was observed at adequate rates for prevention to be reliably assessed. If workers in higher noise environments were identified, it is possible that STS would accrue more quickly, but the ethical issues regarding retraining on HPD use would need to be clearly addressed with the oversight bodies to assure that required HPD refitting and retraining would occur regardless of study enrollment.

These challenges do not mean that NIHL prevention is not feasible to investigate in workers, but rather, that the study endpoints must be both clinically relevant and feasible. The very important issue of longitudinal clinical trials for NIHL prevention is a major challenge. As presented in Figure 1, most NIHL occurs over years and decades. Yet, new pharmacologic agents usually cannot be tested over years and decades both because of the exorbitant costs of such an approach and because patents would expire during that time course, meaning the pharmaceutical company could never recover its investments.

Many additional factors could be measured or controlled for in clinical trials with workers, particularly with respect to HPD use. A small number of studies noted recruitment of workers not wearing HPDs (34, 74). Readers are again reminded that investigators have an ethical obligation to encourage or require HPDs in high-risk environments even though their use can result in data variability and reduce the likelihood of sufficient hearing loss for testing an

otoprotectant. For those studies in which HPDs were worn by some or all participants, variation in the attenuation achieved during HPD use likely varied significantly from person to person. Thus, HPD fit and the variable achieved attenuation are major unmeasured factors across investigations.

The literature on the use of fit testing to document achieved attenuation outcomes (127, 166, 188) may guide clinical trial design through insights into the measurement and documentation of worker HPD attenuation at training. For fit testing to be useful, attenuation at the time of fit testing will need to be correlated with individual attenuation on an on-going basis. Additional research is needed to assess whether worker attenuation measured at the time of fit testing is representative of daily attenuation and is more informative for hearing outcomes than simple recording of the noise reduction rating of the provided HPD.

Summary and Conclusions

The audiogram has clearly served as the primary functional tool for NIHL otoprotection studies, although average threshold shift and rate of STS have both been used. A variety of secondary outcomes were discussed, including DPOAEs, TEOAEs, EHF hearing, hearing in noise, evoked potentials, tinnitus surveys, and PROMs.

Inclusion of all measures is challenging in a TTS study, as noise injury will be progressively recovering across the course of the battery. Inclusion of all measures may also be challenging in PTS studies, however, as study site logistics, particularly in military settings, often provide limited access to participants. The longer the protocol, the lower the recruitment and the greater the attrition. In addition, many of these populations may be restricted to testing on or near their work sites with very limited space and facilities available to the research team. Efforts to develop minimum standards will need to balance study site logistics and limitations against the information gained by each study metric to assure that potentially lengthy batteries do not compromise the ability to conduct clinical trials.

Expert consensus set forward in Campbell *et al.* (19) suggests that the prevention of shifts ≥10 dB HL at one or more frequencies is adequate and appropriate for studies of TTS or PTS prevention. Here, it is advocated that the rate of shifts meeting this criterion be reported, and subtraction of the rate of improvements ≥10 dB should be considered, as discussed previously by Dobie (32). This does not preclude inclusion of other study metrics as either primary or secondary outcomes, but would assure inclusion of a single consistent criterion across investigations.

Expanding on this proposal, it is suggested that inclusion of speech-in-noise tests would provide additional evidence of the clinical significance of any observed protection, as speech-in-noise deficits can be reliably detected even in the absence of TTS or PTS. The inclusion of DPOAE and/or EHF testing as secondary outcomes would provide insight into the integrity of the OHC population across the length of the cochlea and yield insight into specific otopathologies that are commonly associated with both threshold shift and speech-in-noise difficulties [per Parker (152)].

Readers are reminded that many of the studies to date were not conducted under FDA oversight, and regardless of what metrics have been used previously, the FDA is responsible for approving clinically meaningful outcomes and statistical analysis plans for new studies. It is incumbent on the study team to be prepared to address not only study power and statistical differences for any proposed functional metric, but also the clinical significance of the protection predicted to be measured using those metrics.

The review by Cousins (30) provides a comprehensive explanation of the viability of the ear as a therapeutic target, and the review by Schilder *et al.* (164) describes the large number of commercial entities that are investing in drug discovery in the inner ear. Consensus on clinical trial endpoints is urgently needed to advance drugs through the development phase and the regulatory process. As introduced at the start of this document, the FDA is a key stakeholder in that they oversee the regulatory process and make decisions regarding labeling claims based on study data. As the number of clinical trials under FDA oversight grows, and ClinicalTrials.gov study listings expand (commensurate with the mandatory listing process for studies that are conducted under an IND), insights into the acceptability of proposed endpoints by the FDA will improve.

References

1. Almadhoob A and Ohlsson A. Sound reduction management in the neonatal intensive care unit for preterm or very low birth weight infants. *Cochrane Database Syst Rev* 1: Cd010333, 2020.
2. Alvord LS. Cochlear dysfunction in ''normal-hearing'' patients with history of noise exposure. *Ear Hear* 4: 247–250, 1983.
3. American Academy of Audiology. Position statement and clinical practice guidelines: ototoxicity monitoring. 2009. https://audiology-web.s3.amazonaws.com/migrated/OtoMonGuidelines.pdf_539974c40999c1.58842217.pdf Last accessed July 12, 2021.

4. American Academy of Audiology. Clinical consensus document: audiological services for musicians and music industry personnel. 2020. https://www.audiology.org/sites/default/files/publications/resources/Musicians%20Consensus%20Doc_Final_1.23.20.pdf Last accessed April 2, 2020.

5. American Speech-Language-Hearing Association. Guidelines for the audiologic management of individuals receiving cochleotoxic drug therapy. *ASHA* 36(Suppl. 12): 11–19, 1994.

6. Attias J, Sapir S, Bresloff I, Reshef-Haran I, and Ising H. Reduction in noise-induced temporary threshold shift in humans following oral magnesium intake. *Clin Otolaryngol* 29: 635–641, 2004.

7. Attias J, Weisz G, Almog S, Shahar A, Wiener M, Joachims Z, Netzer A, Ising H, Rebentisch E, and Guenther T. Oral magnesium intake reduces permanent hearing loss induced by noise exposure. *Am J Otolaryngol* 15: 26–32, 1994.

8. Baguley D and Norman M. Tinnitus handicap inventory. *J Am Acad Audiol* 12: 379–380, 2001.

9. Baguley DM and Andersson G. Factor analysis of the Tinnitus Handicap Inventory. *Am J Audiol* 12: 31–34, 2003.

10. Baguley DM, Humphriss RL, and Hodgson CA. Convergent validity of the tinnitus handicap inventory and the tinnitus questionnaire. *J Laryngol Otol* 114: 840–843, 2000.

11. Balsan MJ, Burns J, Kimock F, Hirsch E, Unger A, Telesco R, and Bloch-Salisbury E. A pilot study to assess the safety, efficacy and ease of use of a novel hearing protection device for hospitalized neonates. *Early Hum Dev* 156: 105365, 2021.

12. Beken S, Önal E, Gündüz B, Çakir U, Karagöz İ, and Kemaloğlu YK. Negative effects of noise on NICU graduates' cochlear functions. *Fetal Pediatr Pathol* 40: 295–304, 2021.

13. Beukes EW, Baguley DM, Allen PM, Manchaiah V, and Andersson G. Audiologist-guided internet-based cognitive behavior therapy for adults with tinnitus in the United Kingdom: a randomized controlled trial. *Ear Hear* 39: 423–433, 2018.

14. Bharadwaj HM, Mai AR, Simpson JM, Choi I, Heinz MG, and Shinn-Cunningham BG. Non-invasive assays of cochlear synaptopathy—candidates and considerations. *Neuroscience* 407: 53–66, 2019.

15. Bramhall N, Beach EF, Epp B, Le Prell CG, Lopez-Poveda EA, Plack CJ, Schaette R, Verhulst S, and Canlon B. The search for noise-induced cochlear synaptopathy in humans: mission impossible? *Hear Res* 377: 88–103, 2019.

16. Brooks B and Knight K. Ototoxicity monitoring in children treated with platinum chemotherapy. *Int J Audiol* 57(sup4): S34–S40, 2018.

17. Brown RE. Experimental studies on the reliability of audiometry. *J Laryngol Otol* 62: 487–524, 1948.

18. Campbell KCM. Phase 2 clinical trials: d-methionine to reduce noise-induced hearing loss. Final report for award W81XWH-11-C-0033, 2016. http://www.dtic.mil/dtic/tr/fulltext/u2/1028742.pdf Last accessed February 28, 2019.

19. Campbell KCM, Hammill T, Hoffer M, Kil J, and Le Prell CG. Guidelines for auditory threshold measurement for significant threshold shift (STS). *Otol Neurotol* 37: e263–e270, 2016.

20. Campbell KCM and Le Prell CG. Drug-induced ototoxicity: diagnosis and monitoring. *Drug Saf* 41: 451–464, 2018.

21. Capriolo C, Viscardi RM, Broderick KA, Nassebeh S, Kochan M, Solanki NS, and Leung JC. Assessment of neonatal intensive care unit sound exposure using a smartphone application. *Am J Perinatol* 2020 [Epub ahead of print]; DOI: 10.1055/s-0040-1714679.

22. Carcagno S and Plack CJ. Effects of age on electrophysiological measures of cochlear synaptopathy in humans. *Hear Res* 396: 108068, 2020.

23. Carcagno S and Plack CJ. Effects of age on psychophysical measures of auditory temporal processing and speech reception at low and high levels. *Hear Res* 400: 108117, 2021.

24. Carlson DL. American Academy of Audiology response to Gurgel *et al. Otolaryngol Head Neck Surg* 149: 349–350, 2013.

25. Carroll YI, Eichwald J, Scinicariello F, Hoffman HJ, Deitchman S, Radke MS, Themann CL, and Breysse P. Vital signs: noise-induced hearing loss among adults—United States 2011–2012. *MMWR Morb Mortal Wkly Rep* 66: 139–144, 2017.

26. Causon A, Munro KJ, Plack CJ, and Prendergast G. The role of the clinically obtained acoustic reflex as a research tool for subclinical hearing pathologies. *Trends Hear* 24: 2331216520972860, 2020.

27. Chang YS, Bang KH, Jeong B, and Lee GG. Effects of early intratympanic steroid injection in patients with acoustic trauma caused by gunshot noise. *Acta Otolaryngol* 137: 716–719, 2017.

28. Chaturvedi RC, Sharma RK, Lakhera SC, Tiwary RS, and Rai RM. Role of carbogen in protection against noise induced hearing loss in man. *Indian J Med Res* 80: 583–589, 1984.

29. Coles RR, Lutman ME, and Buffin JT. Guidelines on the diagnosis of noise-induced hearing loss for medicolegal purposes. *Clin Otolaryngol Allied Sci* 25: 264–273, 2000.

30. Cousins RP. Medicines discovery for auditory disorders: challenges for industry. *J Acoust Soc Am* 146: 3652–3667, 2019.

31. DiSogra RM. The impact of pharmaceutical side effects on audiological and vestibular measurements. *Semin Hear* 40: 97–103, 2019.

32. Dobie RA. Reliability and validity of industrial audiometry: implications for hearing conservation program design. *Laryngoscope* 93: 906–927, 1983.

33. DoD Instruction 6055.12. Department of Defense Instruction Number 6055.12, Hearing Conservation Program (HCP), December 3, 2010.

34. Doosti A, Lotfi Y, Moossavi A, Bakhshi E, Talasaz AH, and Hoorzad A. Comparison of the effects of N-acetyl-cysteine and ginseng in prevention of noise induced hearing loss in male textile workers. *Noise Health* 16: 223–227, 2014.

35. Etymotic Research. BKB-SIN: Bamford-Kowal-Bench Speech in Noise Test. Elk Grove, IL: Etymotic Research, 2005.

36. Fausti SA, Helt WJ, Gordon JS, Reavis KM, Phillips DS, and Konrad-Martin DL. Audiologic monitoring for ototoxicity and patient management. In: *Pharmacology and Ototoxicity for Audiologists*, edited by Campbell KCM. Clifton Park: Thomson Delmar Learning, 2007, pp. 230–251.

37. Fetoni AR, Garzaro M, Ralli M, Landolfo V, Sensini M, Pecorari G, Mordente A, Paludetti G, and Giordano C. The monitoring role of otoacoustic emissions and oxidative stress markers in the protective effects of antioxidant

administration in noise-exposed subjects: a pilot study. *Med Sci Monit* 15: PR1–PR8, 2009.

38. Garinis AC, Cornell A, Allada G, Fennelly KP, Maggiore RJ, and Konrad-Martin D. Ototoxicity monitoring through the eyes of the treating physician: perspectives from pulmonology and medical oncology. *Int J Audiol* 57: S42–S47, 2018.

39. Garinis AC, Kemph A, Tharpe AM, Weitkamp JH, McEvoy C, and Steyger PS. Monitoring neonates for ototoxicity. *Int J Audiol* 57: S41–S48, 2018.

40. Ge Z, Ma S, Jia X, Zhang L, and Song L. [Study of protective effects on noise-induced hearing impairment by D-methionine tablets pre-loading]. *Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi* 28: 1232–1234, 2014.

41. Gordon JS, Griest SE, Thielman EJ, Carlson KF, Helt WJ, Lewis MS, Blankenship C, Austin DF, Theodoroff SM, and Henry JA. Audiologic characteristics in a sample of recently-separated military Veterans: the Noise Outcomes in Servicemembers Epidemiology Study (NOISE Study). *Hear Res* 349: 21–30, 2017.

42. Graydon K, Waterworth C, Miller H, and Gunasekera H. Global burden of hearing impairment and ear disease. *J Laryngol Otol* 133: 18–25, 2019.

43. Grinn SK and Le Prell CG. Noise-dose estimated with and without pre-cochlear amplification. *J Acoust Soc Am* 146: 3967–3977, 2019.

44. Grinn SK and Le Prell CG. Modeling individual noise-induced hearing loss risk with proxy measurements of external-ear amplification. *J Acoust Soc Am* 149: 3975–3987, 2021.

45. Grinn SK, Wiseman KB, Baker JA, and Le Prell CG. Hidden Hearing Loss? No effect of common recreational noise exposure on cochlear nerve response amplitude in humans. *Front Neurosci* 11: 1–24, 2017.

46. Grose JH, Buss E, and Hall JW, 3rd. Loud music exposure and cochlear synaptopathy in young adults: isolated auditory brainstem response effects but no perceptual consequences. *Trends Hear* 21: 2331216517737417, 2017.

47. Guest H, Munro KJ, Prendergast G, and Plack CJ. Reliability and interrelations of seven proxy measures of cochlear synaptopathy. *Hear Res* 375: 34–43, 2019.

48. Gupta A, Koochakzadeh S, Nguyen SA, Brennan EA, Meyer TA, and Lambert PR. Pharmacological prevention of noise-induced hearing loss: a systematic review. *Otol Neurotol* 32: 2–9, 2020.

49. Gurgel RK, Jackler RK, Dobie RA, and Popelka GR. A new standardized format for reporting hearing outcome in clinical trials. *Otolaryngol Head Neck Surg* 147: 803–807, 2012.

50. Hall DA, Haider H, Kikidis D, Mielczarek M, Mazurek B, Szczepek AJ, and Cederroth CR. Toward a global consensus on outcome measures for clinical trials in tinnitus: report from the first international meeting of the COMiT initiative, November 14, 2014, Amsterdam, The Netherlands. *Trends Hear* 19: 1–7, 2015.

51. Hall DA, Smith H, Hibbert A, Colley V, Haider HF, Horobin A, Londero A, Mazurek B, Thacker B, and Fackrell K. The COMiT'ID study: developing core outcome domains sets for clinical trials of sound-, psychology-, and pharmacology-based interventions for chronic subjective tinnitus in adults. *Trends Hear* 22: 1–16, 2018.

52. Hallam RS, Jakes SC, and Hinchcliffe R. Cognitive variables in tinnitus annoyance. *Br J Clin Psychol* 27: 213–222, 1988.

53. Hammill TL. An evidence-base and implementation framework for promoting best practices in pharmaceutical interventions for hearing loss (PIHL) [Dissertation]. Austin, Texas: The University of Texas at Austin, 2017.

54. Hammill TL. A review of the progress and pitfalls of FDA policy process: planning a pathway for pharmaceutical interventions for hearing loss development. *Hear Res* 349: 172–176, 2017.

55. Hammill TL and Campbell KC. Protection for medication-induced hearing loss: the state of the science. *Int J Audiol* 57: S67–S75, 2018.

56. Hecht QA, Hammill TL, Calamia PT, Smalt CJ, and Brungart DS. Characterization of acute hearing changes in United States military populations. *J Acoust Soc Am* 146: 3839–3848, 2019.

57. Heffernan E, Weinstein BE, and Ferguson MA. Application of Rasch analysis to the evaluation of the measurement properties of the Hearing Handicap Inventory for the Elderly. *Ear Hear* 41: 1125–1134, 2020.

58. Henry JA. ''Measurement'' of tinnitus. *Otol Neurotol* 37: e276–e285, 2016.

59. Henry JA, Griest S, Thielman E, McMillan G, Kaelin C, and Carlson KF. Tinnitus Functional Index: development, validation, outcomes research, and clinical application. *Hear Res* 334: 58–64, 2016.

60. Henry JA, McMillan G, Dann S, Bennett K, Griest S, Theodoroff S, Silverman SP, Whichard S, and Saunders G. Tinnitus management: randomized controlled trial comparing extended-wear hearing aids, conventional hearing aids, and combination instruments. *J Am Acad Audiol* 28: 546–561, 2017.

61. Hickox AE and Liberman MC. Is noise-induced cochlear neuropathy key to the generation of hyperacusis or tinnitus? *J Neurophysiol* 111: 552–564, 2014.

62. Hoben R, Easow G, Pevzner S, and Parker MA. Outer hair cell and auditory nerve function in speech recognition in quiet and in background noise. *Front Neurosci* 11: 157, 2017.

63. Hope AJ, Luxon LM, and Bamiou DE. Effects of chronic noise exposure on speech-in-noise perception in the presence of normal audiometry. *J Laryngol Otol* 127: 233–238, 2013.

64. International Standard Organization. Acoustics: estimation of noise-induced hearing loss (ISO-1999). International Standard Organization, Geneva, Switzerland, 2013.

65. Jackler R, Gurgel R, Dobie R, and Popelka G. Reply to Dr Carlson's letter: a new standardized format for reporting hearing outcome in clinical trials. *Otolaryngol Head Neck Surg* 149: 350, 2013.

66. Jamesdaniel S, Elhage KG, Rosati R, Ghosh S, Arnetz B, and Blessman J. Tinnitus and self-perceived hearing handicap in firefighters: a cross-sectional study. *Int J Environ Res Public Health* 16: 3958, 2019.

67. Jansen EJ, Helleman HW, Dreschler WA, and de Laat JA. Noise induced hearing loss and other hearing complaints among musicians of symphony orchestras. *Int Arch Occup Environ Health* 82: 153–164, 2009.

68. Joachims Z, Netzer A, Ising H, Rebentisch E, Attias J, Weisz G, and Gunther T. Oral magnesium supplementation as prophylaxis for noise-induced hearing loss: results of a double blind field study. *Schriftenr Ver Wasser Boden Lufthyg* 88: 503–516, 1993.

69. Joglekar SS, Lipscomb DM, and Shambaugh GE, Jr. Effects of oxygen inhalation on noise-induced threshold shifts in humans and chinchillas. *Arch Otolaryngol* 103: 574–578, 1977.

70. Johannesen PT, Buzo BC, and Lopez-Poveda EA. Evidence for age-related cochlear synaptopathy in humans unconnected to speech-in-noise intelligibility deficits. *Hear Res* 374: 35–48, 2019.

71. Jokel C, Yankaskas K, and Robinette MB. Noise of military weapons, ground vehicles, planes and ships. *J Acoust Soc Am* 146: 3832–3838, 2019.

72. Kamalski DM, Hoekstra CE, van Zanten BG, Grolman W, and Rovers MM. Measuring disease-specific health-related quality of life to evaluate treatment outcomes in tinnitus patients: a systematic review. *Otolaryngol Head Neck Surg* 143: 181–185, 2010.

73. Kamerer AM, Kopun JG, Fultz SE, Neely ST, and Rasetshwane DM. Reliability of measures intended to assess threshold-independent hearing disorders. *Ear Hear* 40: 1267–1279, 2019.

74. Kapoor N, Mani KV, Shyam R, Sharma RK, Singh AP, and Selvamurthy W. Effect of vitamin E supplementation on carbogen-induced amelioration of noise induced hearing loss in man. *Noise Health* 13: 452–458, 2011.

75. Kemp DT. Otoacoustic emissions, their origin in cochlear function, and use. *Br Med Bull* 63: 223–241, 2002.

76. Kerns E, Masterson EA, Themann CL, and Calvert GM. Cardiovascular conditions, hearing difficulty, and occupational noise exposure within US industries and occupations. *Am J Ind Med* 61: 477–491, 2018.

77. Kerr MJ, Neitzel RL, Hong O, and Sataloff RT. Historical review of efforts to reduce noise-induced hearing loss in the United States. *Am J Ind Med* 60: 569–577, 2017.

78. Kil J, Lobarinas E, Spankovich C, Griffiths S, Antonelli PJ, Lynch ED, and Le Prell CG. Safety and efficacy of Ebselen for the prevention of noise-induced hearing loss: a randomized double blind placebo-controlled phase 2 clinical trial. *Lancet* 390: 969–979, 2017.

79. Killion MC, Niquette PA, Gudmundsen GI, Revit LJ, and Banerjee S. Development of a quick speech-in-noise test for measuring signal-to-noise ratio loss in normal-hearing and hearing-impaired listeners. *J Acoust Soc Am* 116: 2395–2405, 2004.

80. King KA and Brewer CC. Clinical trials, ototoxicity grading scales and the audiologist's role in therapeutic decision making. *Int J Audiol* 57: S89–S98, 2018.

81. Konrad-Martin D, Poling GL, Dreisbach LE, Reavis KM, McMillan GP, Lapsley Miller JA, and Marshall L. Serial monitoring of otoacoustic emissions in clinical trials. *Otol Neurotol* 37: e286–e294, 2016.

82. Konrad-Martin D, Reavis K, McMillan G, and Dille M. Multivariate DPOAE metrics for identifying changes in hearing: perspectives from ototoxicity monitoring. *Int J Audiol* 1 Suppl 1: S51–S62, 2012.

83. Kopke R, Slade MD, Jackson R, Hammill T, Fausti S, Lonsbury-Martin B, Sanderson A, Dreisbach L, Rabinowitz P, Torre P, 3rd, and Balough B. Efficacy and safety of N-acetylcysteine in prevention of noise induced hearing loss: a randomized clinical trial. *Hear Res* 323: 40–50, 2015.

84. Kraak JT, van Dam TF, van Leeuwen LM, Kramer SE, and Merkus P. The Otology Questionnaire Amsterdam: a generic patient-reported outcome measure about the severity and impact of ear complaints. Validation, reliability and responsiveness. *Clin Otolaryngol* 45: 506–516, 2020.

85. Kramer S, Dreisbach L, Lockwood J, Baldwin K, Kopke RD, Scranton S, and O'Leary M. Efficacy of the antioxidant N-acetylcysteine (NAC) in protecting ears exposed to loud music. *J Am Acad Audiol* 17: 265–278, 2006.

86. Kujala T, Shtyrov Y, Winkler I, Saher M, Tervaniemi M, Sallinen M, Teder-Salejarvi W, Alho K, Reinikainen K, and Naatanen R. Long-term exposure to noise impairs cortical sound processing and attention control. *Psychophysiology* 41: 875–881, 2004.

87. Kujawa SG and Liberman MC. Adding insult to injury: cochlear nerve degeneration after ''temporary'' noise-induced hearing loss. *J Neurosci* 29: 14077–14085, 2009.

88. Kujawa SG and Liberman MC. Translating animal models to human therapeutics in noise-induced and age-related hearing loss. *Hear Res* 377: 44–52, 2019.

89. Kuk FK, Tyler RS, Russell D, and Jordan H. The psychometric properties of a tinnitus handicap questionnaire. *Ear Hear* 11: 434–445, 1990.

90. Kumar UA, Ameenudin S, and Sangamanatha AV. Temporal and speech processing skills in normal hearing individuals exposed to occupational noise. *Noise Health* 14: 100–105, 2012.

91. Laffoon SM, Stewart M, Zheng Y, and Meinke DK. Conventional audiometry, extended high-frequency audiometry, and DPOAEs in youth recreational firearm users. *Int J Audiol* 58: S40–S48, 2019.

92. Le Prell CG. Current issues in clinical and translational research in the hearing sciences, audiology, and otolaryngology. In: *Translational Research in Audiology and the Hearing Sciences, Springer Handbook of Auditory Research*, edited by Le Prell CG, Lobarinas E, Fay RR, and Popper AN. New York: Springer, 2016, pp. 19–50.

93. Le Prell CG. Effects of noise exposure on auditory brainstem response and speech-in-noise tasks: a review of the literature. *Int J Audiol* 58: S3–S32, 2019.

94. Le Prell CG. Otoprotectants: from research to clinical application. *Semin Hear* 40: 162–176, 2019.

95. Le Prell CG. Investigational medicinal products for the inner ear: review of clinical trial characteristics in ClinicalTrials.gov. *J Am Acad Audiol*, in press.

96. Le Prell CG. Noise-induced hearing loss. In: *Bailey's Head & Neck Surgery: Otolaryngology, 6th edition*, edited by Roden C, Gray S, Ha P, Limb C, Park S, Richter G. Philadelphia: Wolters Kluwer; in press.

97. Le Prell CG and Brungart DS. Speech-in-noise tests and supra-threshold auditory evoked potentials as metrics for noise damage and clinical trial outcome measures. *Otol Neurotol* 37: e295–e302, 2016.

98. Le Prell CG and Campbell KCM. Clinical test paradigms and problems: human otoprotection studies. In: *Advances in Audiology, Speech Pathology, and Hearing Science, Volume 2: Otoprotection, Regeneration and Telemedicine*, edited by Hatzopoulos S, Ciorba A, and Krumm M. New Jersey: Apple Academic Press, 2020, pp. 233–269.

99. Le Prell CG and Clavier OH. Effects of noise on speech recognition: challenges for communication by service members. *Hear Res* 349: 76–89, 2017.

100. Le Prell CG, Dell S, Hensley BN, Hall JWI, Campbell KCM, Antonelli PA, Green GE, Miller JM, and Guire K. Digital music exposure reliably induces temporary

threshold shift (TTS) in normal hearing human subjects. *Ear Hear* 33: e44–e58, 2012.

101. Le Prell CG, Fulbright A, Spankovich C, Griffiths S, Lobarinas E, Campbell KCM, Antonelli PJ, Green GE, Guire K, and Miller JM. Dietary supplement comprised of β-carotene, vitamin C, vitamin E, and magnesium: failure to prevent music-induced temporary threshold shift. *Audiol Neurotol Extra* 6: 20–39, 2016.

102. Le Prell CG, Hamill T, and Murphy WJ. Noise-induced hearing loss and its prevention: integration of data from animal models and human clinical trials. *J Acoust Soc Am* 146: 4051–4074, 2019.

103. Le Prell CG, Hamill T, and Murphy WJ. Noise-induced hearing loss: translating risk from animal models to real-world environments. *J Acoust Soc Am* 146: 3646–3651, 2019.

104. Le Prell CG, Johnson A-C, Lindblad A-C, Skjönsberg A, Ulfendahl M, Guire K, Green GE, Campbell KCM, and Miller JM. Increased vitamin plasma levels in Swedish military personnel treated with nutrients prior to automatic weapon training. *Noise Health* 13: 432–443, 2011.

105. Le Prell CG and Lobarinas E. Strategies for assessing antioxidant efficacy in clinical trials. In: *Oxidative Stress in Applied Basic Research and Clinical Practice: Free Radicals in ENT Pathology*, edited by Miller JM, Le Prell CG, and Rybak LP. New York: Humana Press, 2015, pp. 163–192.

106. Le Prell CG and Miller JM. The role of oxidative stress in hearing loss. In: *Oxidative Stress and Antioxidant Protection: The Science of Free Radical Biology & Disease*, edited by Armstrong D and Stratton RD. New Jersey: John Wiley & Sons, Inc., 2016, pp. 115–131.

107. Le Prell CG, Roth K, and Campbell KCM. Towards clinical pharmacologic otoprotection. In: *Advances in Audiology, Speech Pathology, and Hearing Science, Volume 2: Otoprotection, Regeneration and Telemedicine*, edited by Hatzopoulos S, Ciorba A, and Krumm M. New Jersey: Apple Academic Press, 2020, pp. 179–231.

108. Le Prell CG, Yang Q, and Harris J. Modification of digital music files for use in human temporary threshold shift studies. *J Acoust Soc Am Expr Lett* 130: EL142–EL146, 2011.

109. Le TN, Straatman LV, Lea J, and Westerberg B. Current insights in noise-induced hearing loss: a literature review of the underlying mechanism, pathophysiology, asymmetry, and management options. *J Otolaryngol Head Neck Surg* 46: 41, 2017.

110. Leger AC, Moore BC, and Lorenzi C. Abnormal speech processing in frequency regions where absolute thresholds are normal for listeners with high-frequency hearing loss. *Hear Res* 294: 95–103, 2012.

111. Liberman MC, Epstein MJ, Cleveland SS, Wang H, and Maison SF. Toward a differential diagnosis of hidden hearing loss in humans. *PLoS One* 11: e0162726, 2016.

112. Lin CY, Wu JL, Shih TS, Tsai PJ, Sun YM, Ma MC, and Guo YL. N-Acetyl-cysteine against noise-induced temporary threshold shift in male workers. *Hear Res* 269: 42–47, 2010.

113. Lin HW, Furman AC, Kujawa SG, and Liberman MC. Primary neural degeneration in the guinea pig cochlea after reversible noise-induced threshold shift. *J Assoc Res Otolaryngol* 12: 605–616, 2011.

114. Lindblad AC, Rosenhall U, Olofsson A, and Hagerman B. The efficacy of N-acetylcysteine to protect the human cochlea from subclinical hearing loss caused by impulse noise: a controlled trial. *Noise Health* 13: 392–401, 2011.

115. Lobarinas E, Scott R, Spankovich C, and Le Prell CG. Differential effects of suppressors on hazardous sound pressure levels generated by AR-15 rifles: considerations for recreational shooters, law enforcement, and the military. *Int J Audiol* 55 Suppl 1: S59–S71, 2016.

116. Lord SG. Monitoring protocols for cochlear toxicity. *Semin Hear* 40: 122–143, 2019.

117. Lynch ED, Kil J, and Le Prell CG. Human clinical studies in noise-induced hearing loss. In: *Translational Research in Audiology and the Hearing Sciences, Springer Handbook of Auditory Research*, edited by Le Prell CG, Lobarinas E, Fay RR, and Popper AN. New York: Springer, 2016, pp. 105–139.

118. Makary CA, Shin J, Kujawa SG, Liberman MC, and Merchant SN. Age-related primary cochlear neuronal degeneration in human temporal bones. *J Assoc Res Otolaryngol* 12: 711–717, 2011.

119. Meikle MB, Henry JA, Griest SE, Stewart BJ, Abrams HB, McArdle R, Myers PJ, Newman CW, Sandridge S, Turk DC, Folmer RL, Frederick EJ, House JW, Jacobson GP, Kinney SE, Martin WH, Nagler SM, Reich GE, Searchfield G, Sweetow R, and Vernon JA. The tinnitus functional index: development of a new clinical measure for chronic, intrusive tinnitus. *Ear Hear* 33: 153–176, 2012.

120. Meinke DK, Finan DS, Flamme GA, Murphy WJ, Stewart M, Lankford JE, and Tasko S. Prevention of noise-induced hearing loss from recreational firearms. *Semin Hear* 38: 267–281, 2017.

121. Mepani AM, Kirk SA, Hancock KE, Bennett K, de Gruttola V, Liberman MC, and Maison SF. Middle ear muscle reflex and word recognition in ''normal-hearing'' adults: evidence for cochlear synaptopathy? *Ear Hear* 41: 25–38, 2020.

122. Mepani AM, Verhulst S, Hancock KE, Garrett M, Vasilkov V, Bennett K, de Gruttola V, Liberman MC, and Maison SF. Envelope following responses predict speech-in-noise performance in normal-hearing listeners. *J Neurophysiol* 125: 1213–1222, 2021.

123. Moon IS. Noise-induced hearing loss caused by gunshot in South Korean military service. *Mil Med* 172: 421–425, 2007.

124. Moore BCJ. Diagnosis and quantification of military noise-induced hearing loss. *J Acoust Soc Am* 148: 884, 2020.

125. Moore BCJ and von Gablenz P. Sensitivity and specificity of a method for diagnosis of military noise-induced hearing loss. *J Acoust Soc Am* 149: 62, 2021.

126. Motlagh Zadeh L, Silbert NH, Sternasty K, Swanepoel W, Hunter LL, and Moore DR. Extended high-frequency hearing enhances speech perception in noise. *Proc Natl Acad Sci U S A* 116: 23753–23759, 2019.

127. Murphy WJ, Themann CL, and Murata TK. Hearing protector fit testing with off-shore oil-rig inspectors in Louisiana and Texas. *Int J Audiol* 55: 688–698, 2016.

128. NCT00552786. Antioxidation Medication for Noise-induced Hearing Loss. http://clinicaltrials.gov/ct2/show/NCT00808470 Last accessed December 29, 2020.

129. NCT00808470. Micronutrients to Prevent Noise-induced Hearing Loss. http://clinicaltrials.gov/ct2/show/NCT00808470 Last accessed December 29, 2020.

130. NCT01444846. Otoprotection with SPI-1005. http://clinicaltrials.gov/ct2/show/NCT01444846 Last accessed December 29, 2020.

131. NCT02049073. Prevention of Noise-induced Hearing Loss. http://clinicaltrials.gov/ct2/show/NCT02049073 Last accessed December 29, 2020.

132. NCT02257983. Protective Effects of EPI-743 on Noise-Induced Hearing Loss. http://clinicaltrials.gov/ct2/show/NCT02257983 Last accessed December 29, 2020.

133. NCT02779192. A Phase 2b Study of SPI-1005 to Prevent Acute Noise Induced Hearing Loss (PANIHL). https://clinicaltrials.gov/ct2/show/NCT02779192 Last accessed December 29, 2020.

134. NCT02903355. Phase 3 Clinical Trial: D-Methionine to Reduce Noise-Induced Hearing Loss (NIHL). https://clinicaltrials.gov/ct2/show/NCT02903355 Last accessed December 22, 2020.

135. NCT03834714. Noise Exposure and Near-Infrared Light. https://clinicaltrials.gov/ct2/show/NCT03834714 Last accessed December 29, 2020.

136. NCT04129775. OTO-413 in Subjects with Speech-in-Noise Hearing Impairment. https://clinicaltrials.gov/ct2/show/NCT04129775 Last accessed February 12, 2021.

137. NCT04462198. Phase I/IIa Study Evaluating Safety and Efficacy of an Intratympanic Dose of PIPE-505 in Subjects with Hearing Loss. https://clinicaltrials.gov/ct2/show/NCT04462198 Last accessed February 12, 2021.

138. NCT04768569. Noise-Induced Hearing Loss-Acute Exposure Treatment (PINIHL-AET). https://clinicaltrials.gov/ct2/show/NCT04768569 Last accessed June 11, 2021.

139. NCT04774250. Noise-Induced Hearing Loss-Acute Exposure Treatment (UA) (PINIHL-AET). https://clinicaltrials.gov/ct2/show/NCT04774250 Last accessed June 11, 2021.

140. Nelson DI, Nelson RY, Concha-Barrientos M, and Fingerhut M. The global burden of occupational noise-induced hearing loss. *Am J Ind Med* 48: 446–458, 2005.

141. Newman CW, Jacobson GP, and Spitzer JB. Development of the Tinnitus Handicap Inventory. *Arch Otolaryngol Head Neck Surg* 122: 143–148, 1996.

142. Newman CW, Sandridge SA, and Jacobson GP. Assessing outcomes of tinnitus intervention. *J Am Acad Audiol* 25: 76–105, 2014.

143. Newman CW, Weinstein BE, Jacobson GP, and Hug GA. The Hearing Handicap Inventory for Adults: psychometric adequacy and audiometric correlates. *Ear Hear* 11: 430–433, 1990.

144. Newman CW, Weinstein BE, Jacobson GP, and Hug GA. Test-retest reliability of the hearing handicap inventory for adults. *Ear Hear* 12: 355–357, 1991.

145. Newman CW, Wharton JA, and Jacobson GP. Retest stability of the tinnitus handicap questionnaire. *Ann Otol Rhinol Laryngol* 104: 718–723, 1995.

146. NIOSH. Criteria for a Recommended Standard, Occupational Noise Exposure, DHHS (NIOSH) Publication No.98–126. DHHS/CDC/NIOSH, Cincinnati, OH, 1998.

147. Niskar AS, Kieszak SM, Holmes AE, Esteban E, Rubin C, and Brody DJ. Estimated prevalence of noise-induced hearing threshold shifts among children 6 to 19 years of age: the Third National Health and Nutrition Examination Survey, 1988–1994, United States. *Pediatrics* 108: 40–43, 2001.

148. Occupational Safety and Health Administration. 29 CFR 1910.95. Occupational noise exposure: hearing conservation amendment; final rule, January 16, 1981. *Fed Regist* 46: 4078–4179, 1981.

149. Oishi N and Schacht J. Emerging treatments for noise-induced hearing loss. *Expert Opin Emerg Drugs* 16: 235–245, 2011.

150. OSHA. 29 CFR 1910.95. Occupational Noise Exposure; Hearing Conservation Amendment; Final Rule, effective March 8, 1983; 1983.

151. Paken J, Govender CD, Pillay M, and Sewram V. A review of cisplatin-associated ototoxicity. *Semin Hear* 40: 108–121, 2019.

152. Parker MA. Identifying three otopathologies in humans. *Hear Res* 398: 108079, 2020.

153. Phillips SL, Henrich VC, and Mace ST. Prevalence of noise-induced hearing loss in student musicians. *Int J Audiol* 49: 309–316, 2010.

154. Pienkowski M. On the etiology of listening difficulties in noise despite clinically normal audiograms. *Ear Hear* 38: 135–148, 2017.

155. Plack CJ, Barker D, and Prendergast G. Perceptual consequences of ''hidden'' hearing loss. *Trends Hear* 18: 2331216514550621, 2014.

156. Plack CJ, Leger A, Prendergast G, Kluk K, Guest H, and Munro KJ. Toward a diagnostic test for hidden hearing loss. *Trends Hear* 20: 2331216516657466, 2016.

157. Prendergast G, Millman RE, Guest H, Munro KJ, Kluk K, Dewey RS, Hall DA, Heinz MG, and Plack CJ. Effects of noise exposure on young adults with normal audiograms II: behavioral measures. *Hear Res* 356: 74–86, 2017.

158. Prendergast G, Tu W, Guest H, Millman RE, Kluk K, Couth S, Munro KJ, and Plack CJ. Supra-threshold auditory brainstem response amplitudes in humans: test-retest reliability, electrode montage and noise exposure. *Hear Res* 364: 38–47, 2018.

159. Quaranta A, Scaringi A, Bartoli R, Margarito MA, and Quaranta N. The effects of 'supra-physiological' vitamin B12 administration on temporary threshold shift. *Int J Audiol* 43: 162–165, 2004.

160. Quaranta N, Dicorato A, Matera V, D'Elia A, and Quaranta A. The effect of alpha-lipoic acid on temporary threshold shift in humans: a preliminary study. *Acta Otorhinolaryngol Ital* 32: 380–385, 2012.

161. Robinette MS. Clinical observations with evoked otoacoustic emissions at Mayo Clinic. *J Am Acad Audiol* 14: 213–224, 2003.

162. Rodríguez Valiente A, Trinidad A, García Berrocal JR, Górriz C, and Ramírez Camacho R. Extended high-frequency (9–20 kHz) audiometry reference thresholds in 645 healthy subjects. *Int J Audiol* 53: 531–545, 2014.

163. Ryan AF, Kujawa SG, Hammill T, Le Prell C, and Kil J. Temporary and permanent noise-induced threshold shifts: a review of basic and clinical observations. *Otol Neurotol* 37: e271–e275, 2016.

164. Schilder AGM, Su MP, Blackshaw H, Lustig L, Staecker H, Lenarz T, Safieddine S, Gomes-Santos CS, Holme R, and Warnecke A. Hearing protection, restoration, and regeneration: an overview of emerging therapeutics for inner ear and central hearing disorders. *Otol Neurotol* 40: 559–570, 2019.

165. Schilder AGM, Su MP, Mandavia R, Anderson CR, Landry E, Ferdous T, and Blackshaw H. Early phase trials of novel hearing therapeutics: avenues and opportunities. *Hear Res* 380: 175–186, 2019.

166. Schulz TY. Individual fit-testing of earplugs: a review of uses. *Noise Health* 13: 152–162, 2011.

167. Sha SH and Schacht J. Emerging therapeutic interventions against noise-induced hearing loss. *Expert Opin Investig Drugs* 26: 85–96, 2017.

168. Smith SW, Ortmann AJ, and Clark WW. Noise in the neonatal intensive care unit: a new approach to examining acoustic events. *Noise Health* 20: 121–130, 2018.

169. Staecker H, Klickstein L, and Brough DE. Developing a molecular therapeutic for hearing loss. In: *Translational Research in Audiology and the Hearing Sciences, Springer Handbook of Auditory Research*, edited by Le Prell CG, Lobarinas E, Fay RR, and Popper AN. New York: Springer, 2016, pp. 197–217.

170. Staffa P, Cambi J, Mezzedimi C, Passali D, and Bellussi L. Activity of coenzyme Q 10 (Q-Ter multicomposite) on recovery time in noise-induced hearing loss. *Noise Health* 16: 265–269, 2014.

171. Stelmachowicz PG, Beauchaine KA, Kalberer A, and Jesteadt W. Normative thresholds in the 8- to 20-kHz range as a function of age. *J Acoust Soc Am* 86: 1384–1391, 1989.

172. Stone MA, Moore BC, and Greenish H. Discrimination of envelope statistics reveals evidence of sub-clinical hearing damage in a noise-exposed population with 'normal' hearing thresholds. *Int J Audiol* 47: 737–750, 2008.

173. Suckfuell M, Canis M, Strieth S, Scherer H, and Haisch A. Intratympanic treatment of acute acoustic trauma with a cell-permeable JNK ligand: a prospective randomized phase I/II study. *Acta Otolaryngol* 127: 938–942, 2007.

174. Summers V, Makashay MJ, Theodoroff SM, and Leek MR. Suprathreshold auditory processing and speech perception in noise: hearing-impaired and normal-hearing listeners. *J Am Acad Audiol* 24: 274–292, 2013.

175. Suter AH. The hearing conservation amendment: 25 years later. *Noise Health* 11: 2–7, 2009.

176. Suzuki J, Corfas G, and Liberman MC. Round-window delivery of neurotrophin 3 regenerates cochlear synapses after acoustic overexposure. *Sci Rep* 6: 24907, 2016.

177. Swan AA, Nelson JT, Swiger B, Jaramillo CA, Eapen BC, Packer M, and Pugh MJ. Prevalence of hearing loss and tinnitus in Iraq and Afghanistan Veterans: a chronic effects of neurotrauma consortium study. *Hear Res* 349: 4–12, 2017.

178. Tak S, Davis RR, and Calvert GM. Exposure to hazardous workplace noise and use of hearing protection devices among US workers—NHANES, 1999–2004. *Am J Ind Med* 52: 358–371, 2009.

179. Themann CL and Masterson EA. Review: occupational noise exposure and hearing loss. *J Acoust Soc Am* 146: 3879–3905, 2019.

180. Theodoroff SM, McMillan GP, Zaugg TL, Cheslock M, Roberts C, and Henry JA. Randomized controlled trial of a novel device for tinnitus sound therapy during sleep. *Am J Audiol* 26: 543–554, 2017.

181. Toppila E, Koskinen H, and Pyykko I. Hearing loss among classical-orchestra musicians. *Noise Health* 13: 45–50, 2011.

182. Toppila E, Pyykko I, Starck J, Tossavainen T, Nyman P, Juhola M, and Oksa P. Protection of inner ear against acute environmental noise with antioxidants, abstracts of the XXII Bárány Society Meeting. *J Vestib Res* 11: 220, 2001.

183. US Department of Veterans Affairs. Veterans Benefits Administration: Annual Benefits Report Fiscal Year 2018. https://www.benefits.va.gov/REPORTS/abr/archive.asp Last accessed June 2, 2021.

184. Van den Borre E, Denys S, van Wieringen A, and Wouters J. The digit triplet test: a scoping review. *Int J Audiol* [Epub ahead of print]; DOI: 10.1080/14992027.2021.1902579.

185. Varela-Nieto I, Murillo-Cuesta S, Calvino M, Cediel R, and Lassaletta L. Drug development for noise-induced hearing loss. *Expert Opin Drug Discov* 15: 1457–1471, 2020.

186. Ventry IM and Weinstein BE. The hearing handicap inventory for the elderly: a new tool. *Ear Hear* 3: 128–134, 1982.

187. Viergever K, Kraak JT, Bruinewoud EM, Ket JCF, Kramer SE, and Merkus P. Questionnaires in otology: a systematic mapping review. *Syst Rev* 10: 119, 2021.

188. Voix J and Hager LD. Individual fit testing of hearing protection devices. *Int J Occup Saf Ergon* 15: 211–219, 2009.

189. Wan G, Gomez-Casati ME, Gigliello AR, Liberman MC, and Corfas G. Neurotrophin-3 regulates ribbon synapse density in the cochlea and induces synapse regeneration after acoustic trauma. *Elife* 3: e03564, 2014.

190. Wang Q, Yang L, Qian M, Hong Y, Wang X, Huang Z, and Wu H. Acute recreational noise-induced cochlear synaptic dysfunction in humans with normal hearing: a prospective cohort study. *Front Neurosci* 15: 659011, 2021.

191. Wartinger F, Malyuk H, and Portnuff CD. Human exposures and their associated hearing loss profiles: music industry professionals. *J Acoust Soc Am* 146: 3906–3910, 2019.

192. Wilson PH, Henry J, Bowen M, and Haralambous G. Tinnitus reaction questionnaire: psychometric properties of a measure of distress associated with tinnitus. *J Speech Hear Res* 34: 197–201, 1991.

193. Wilson RH, Carnell CS, and Cleghorn AL. The Words-in-Noise (WIN) test with multitalker babble and speech-spectrum noise maskers. *J Am Acad Audiol* 18: 522–529, 2007.

194. Witter HL, Deka RC, Lipscomb DM, and Shambaugh GE. Effects of prestimulatory carbogen inhalation on noise-induced temporary threshold shifts in humans and chinchilla. *Am J Otol* 1: 227–232, 1980.

195. World Health Organization. Hearing loss due to recreational exposure to loud sounds: a review. http://apps.who.int/iris/bitstream/10665/154589/1/9789241508513_eng.pdf Last accessed September 2, 2021.

196. Yankaskas K. Prelude: noise-induced tinnitus and hearing loss in the military. *Hear Res* 295: 3–8, 2013.

197. Zhou Y, Zheng G, Zheng H, Zhou R, Zhu X, and Zhang Q. Primary observation of early transtympanic steroid injection in patients with delayed treatment of noise-induced hearing loss. *Audiol Neurootol* 18: 89–94, 2013.

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Abbreviations Used

AAA = American Academy of Audiology
AAO = American Academy of Otolaryngology
ABR = auditory brainstem response
ANF = auditory nerve fiber
ASHA = American Speech-Language-Hearing
Association
BKB-SIN = Bamford-Kowal-Bench
Speech-in-Noise Test
CDER = Center for Drug Evaluation and Research
COMET = Core Outcome Measures in Effectiveness
Trials
CORE = Centre for Outcomes Research
and Evaluation
COSMIN = Consensus-based Standards for the selec-
tion of health Measurement Instruments
dB HL = decibels hearing level
dB SL = decibel sensation level
dBA = A-weighted sound pressure level
DoD = Department of Defense
DOEHRSHC = Defense Occupational and Environmental
Health Readiness System–Hearing Con-
servation
DPOAE = distortion product otoacoustic emission
EHF = extended high frequency
FDA = U.S. Food and Drug Administration
HHIA = Hearing Handicap Inventory for Adults
HHIE = Hearing Handicap Inventory for the Elderly
HINT = Hearing-in-Noise Test
HLAA = Hearing Loss Association of America
HPD = hearing protection device
i.v. = intravenous
IHC = inner hair cell
IND = Investigational New Drug
ITI = intratympanic injection
L_{avg} = average sound level over the period
monitored
M-NIHL = military noise-induced hearing loss

MSHA = Mining Safety and Health Administration
NDA = New Drug Application
NHANES = National Health and Nutrition Examination
Survey
NICU = neonatal intensive care unit
NIHL = noise-induced hearing loss
NIOSH = National Institute of Occupational Safety
and Health
OAE = otoacoustic emission
OHC = outer hair cell
OSHA = Occupational Safety and Health
Administration
PAS = personal audio system
PEL = permissible exposure limit
PIHL = Pharmaceutical Interventions for Hearing
Loss
PROM = patient-reported outcome measure
PTA = pure-tone average
PTS = permanent threshold shift
QuickSin = Quick Speech-in-Noise Test
SDdiff = standard deviation of the test-retest
difference scores
SDS = speech discrimination score
SNR = signal-to-noise ratio
SOC = Significant Ototoxic Change
STS = significant threshold shift
TEOAE = transient evoked otoacoustic emission
TFI = Tinnitus Functional Index
TFOE = transfer function of the open ear
THI = Tinnitus Handicap Inventory
THQ = Tinnitus Handicap Questionnaire
TOMI = Tinnitus Ototoxicity Monitoring
Interview
TQ = Tinnitus Questionnaire
TRQ = Tinnitus Reaction Questionnaire
TTS = temporary threshold shift
WHO = World Health Organization
WIN = Words-in-Noise