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# Noise-Induced Hearing Disorders: Hidden and Not-So-Hidden Injuries, in partnership with American Auditory Society

Colleen Le Prell, PhD

# Colleen Le Prell, PhD

Colleen Le Prell, PhD, is the Head of the Department of Speech, Language, and Hearing and the Director of the recently launched Clinical Trial Unit at the University of Texas at Dallas, where she holds the Emilie and Phil Schepps Professorship in Hearing Science. Dr. Le Prell has received funding from government, industry, and philanthropic sources for research that programmatically advances the understanding and prevention of noise-induced hearing loss. Dr. Le Prell previously served as President for the National Hearing Conservation Association (NHCA), currently serves on the CDC-NIOSH National Occupational Research Agenda (NORA)
Hearing Loss Prevention Cross Sector Council, and is an invited participant in the World Health Organization (WHO) “Make Listening Safe” campaign. She contributes to the peer review process in several Associate Editor roles and serves on the Auditory System (AUD) Study Section for the National Institutes of Health.

# Disclosures

- **Presenter Disclosure:** Financial: Colleen Le Prell is employed by the University of Texas at Dallas. She received an honorarium for this presentation. Research supported by NIH-NIDCD, DoD, American Academy of Audiology, 3M Inc., Sound Pharmaceuticals Inc., Edison Pharmaceuticals, Inc. Presenter has served as paid consultant on clinical trial design questions. Non-financial: Colleen Le Prell is a co-inventor on patents owned by former employer (University of Michigan).
- **Content Disclosure**: This learning event does not focus exclusively on any specific product or service.
- **Sponsor Disclosure:** There is no external sponsor for this course.

# Learning Outcomes

After this course, participants will be able to

- Describe suprathreshold deficits that are commonly captured under the umbrella phrase, “hidden hearing loss,” and their causes.
- Identify diagnostic test batteries relevant for documentation of suprathreshold deficits.
- Summarize the current status of drug development for suprathreshold hearing deficits.

# Agenda

- **Hidden hearing loss terms and definitions**
- Noise-induced cochlear pathology
- Some points of agreement on cochlear synaptopathy, and some open questions
- Existing use of the audiogram, tinnitus surveys, hearing in noise tests, and ABR in clinical trials
- Investigational medicines for hearing loss prevention and hearing restoration

# “Hidden Hearing Loss”

- Kujawa and Liberman (2009) documented noise induced decrease in wave I amplitude in presence of normal ABR thresholds, with loss of cochlear synapses with inner hair cells (“cochlear synapthopathy”)
- Schaette and McAlpine (2011) defined decreased Wave I amplitude with normal ABR thresholds as “hidden hearing loss”
- “Hidden hearing loss” now routinely used for all of the following:
  - Cochlear synaptopathy
  - Decreased Wave I in presence of normal thresholds
  - Various supra-threshold hearing disorders not captured by the audiogram including hearing-in-noise difficulties, tinnitus, hyperacusis
- We can avoid confusion if we use specific terms


- Kujawa SG, Liberman MC. Adding insult to injury: cochlear nerve degeneration after "temporary" noise-induced hearing loss. J Neurosci. 2009 Nov 11;29(45):14077-85.
- Schaette R, McAlpine D. Tinnitus with a normal audiogram: physiological evidence for hidden hearing loss and computational model. J Neurosci. 2011 Sep 21;31(38):13452-7.

# Threshold deficits often OHC related; suprathreshold deficits may be due to loss of OHCs or afferents

## Threshold deficits

- Hearing loss measured using audiogram (or ABR, particularly in rodent studies)
- Threshold elevation
  - NIHL, ARHL
- Clinical gold standard
- **Primary outcome measure in vast majority of clinical trials to date**

## Suprathreshold Deficits

- Hearing-in-noise deficits
- Tinnitus
- Hyperacusis
  - Collectively, NIHD, when associated with noise exposure
- **Not as well represented in clinical trials**

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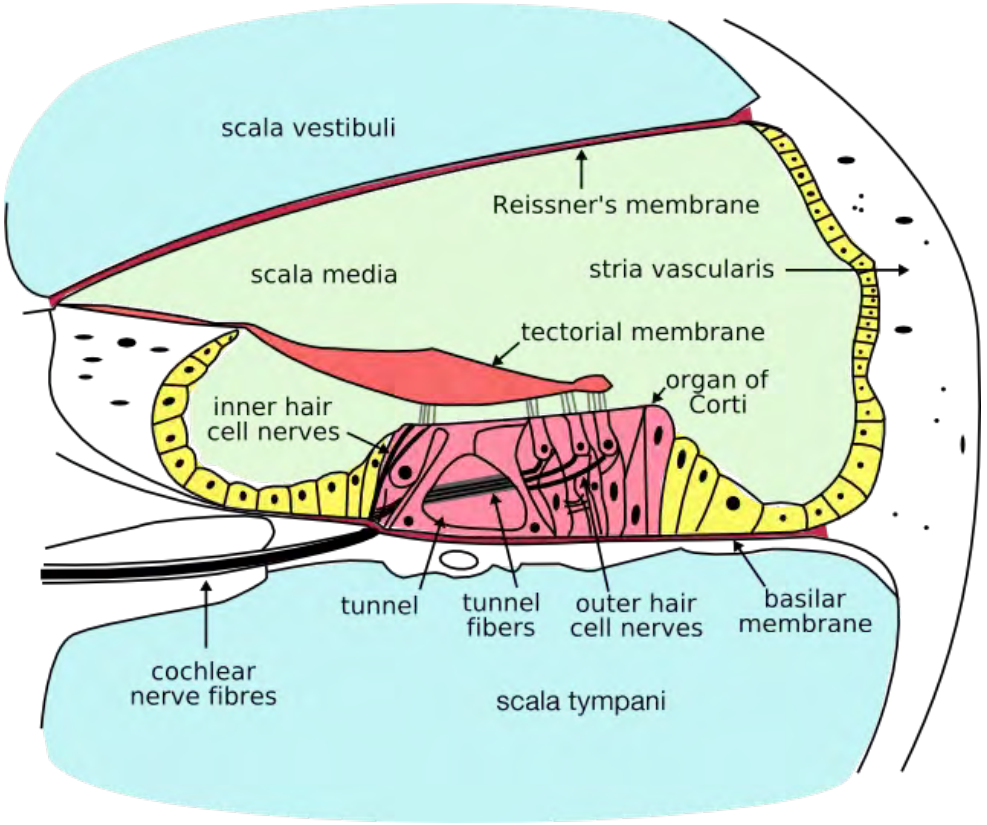
# Noise-induced cochlear pathology

- Injury to OHCs correlated with PTS; 100% OHC loss results in ~40 dB PTS
- Sudden and profound increase in PTS associated with breach of reticular lamina
- Shorter/less intense noise results in neural swelling, damaged stereocilia, swollen or misshapen hair cells
- Permanent loss of synaptic connections between IHCs and auditory nerve after some noise exposures
- Pathology is not strictly mechanical – there is an active metabolic cell stress/cell death process resulting in progressive cell death over days to weeks




From: https://upload.wikimedia.org/wikipedia/commons/0/0c/Cochlea-crosssection.png CCBY 3.0

# Free radicals are normal metabolic byproduct but toxic in excess

- Glucose/sugar and oxygen broken down in cells
- Mitochondria convert nutrients to energy (ATP); this conversion leaks electrons (free radicals)
- Leaked electrons must be neutralized, or damage to cell membranes, mitochondria, and DNA, and cell death, can occur
- Leaked electrons accumulate in outer hair cells after noise exposure (also, aminoglycoside antibiotics and cisplatin therapy)
- Maximum accumulation is at 7-10 days post-noise exposure, a time when outer hair cells are progressing through cell death cycle
- This creates window of opportunity for therapeutic rescue


- For review, see Le Prell, C. G., Yamashita, D., Minami, S., Yamasoba, T., and Miller, J. M. (2007). "Mechanisms of noise-induced hearing loss indicate multiple methods of prevention," Hear. Res. 226, 22-43.
- For delayed cell death, see Yamashita, D., Jiang, H., Schacht, J., and Miller, J. M. (2004). "Delayed production of free radicals following noise exposure," Brain Research 1019, 201-209.
- For post-noise rescue, see Yamashita D, Jiang HY, Le Prell CG, Schacht J, Miller JM. Post-exposure treatment attenuates noise-induced hearing loss. *Neuroscience, 134:633-42,* 2005.

# Agenda

- Hidden hearing loss terms and definitions
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# Not every noise exposure resulting in TTS produces synapse loss

- Studies in animal models show range of synaptic densities in normal controls; in studies with a small number of control ears, control data may not be representative of the normal population
- Some exposures that cause TTS do not cause cochlear synapse loss
- Relationships between TTS, PTS, and cochlear synaptic pathology incompletely understood; PTS appears to be “protective” in that less synapse loss develops in animals with PTS

- For review, see Le Prell, C.G., and Brungart, D.S. (2016). Potential effects of noise on hearing: supra-threshold testing using speech-in-noise and auditory evoked potentials, *Otology & Neurotology, 37: e295-e302*.
- For PTS data see Fernandez KA, Guo D, Micucci S, et al. Noise-induced cochlear synaptopathy with and without sensory cell loss. Neuroscience. 2020 Feb 10;427:43-57.

# Vulnerability to noise-induced synaptopathic injury varies across species

- Mouse: 100-dB SPL OBN x 2 hrs
  - Dose-response studies show PTS with 3 dB level increase, no pathology with 3 dB level decrease
- Chinchilla: similarly vulnerable; 98-99 dB SPL OBN x 2 hrs
  - Synaptic damage plus PTS observed at 100-101 dB SPL (2-dB increase)
- Guinea Pig: 106-dB SPL OBN x 2 hrs
  - PTS observed at 109 dB SPL x 2 hrs (3-dB increase)
- Rat: 109 dB SPL OBN x 2 hrs
  - 106-dB SPL OBN x 2 hrs produced no synaptic injury (3-dB decrease)
- Rhesus macaque: either 108-dB SPL NBN x 4 hrs (50 Hz noise band centered at 2 kHz) or 120 dB SPL OBN x 4 hrs
- Noise-injury data from humans are mixed both in their design and in their results

For review see Le Prell, C. G. (2019). "Effects of noise exposure on auditory brainstem response and speech-in-noise tasks: A review of the literature," Int. J. Audiol. 58, S3-S32.

# Humans are at risk for cochlear synaptopathy

- Vulnerability to noise-induced synapse loss is unclear in humans; we do not know where risk begins or grows (damage-risk criteria needed)
- However, human ABR wave I data are consistent with age-related afferent pathology
- Age-related synapse loss documented in human temporal bones


- Johannesen PT, Buzo BC, Lopez-Poveda EA. Evidence for age-related cochlear synaptopathy in humans unconnected to speech-in-noise intelligibility deficits. Hear Res. 2019 Mar 15;374:35-48.
- Viana LM, O'Malley JT, Burgess BJ, et al. Cochlear neuropathy in human presbycusis: Confocal analysis of hidden hearing loss in post-mortem tissue. Hear Res. 2015 Sep;327:78-88.
- Wu PZ, Liberman LD, Bennett K, et al. Primary neural degeneration in the human cochlea: Evidence for hidden hearing loss in the aging ear. Neuroscience. 2019 Aug 10;407:8-20.

# Individual variability in vulnerability unknown but likely substantive

- Population studies show significant variation in noise-induced hearing loss in humans even when individuals are matched for age and sound exposure
- Individual differences in vulnerability could be related to:
  - Genetics
  - Cardiovascular health
  - Earcanal amplification, middle ear power transfer
  - Dietary nutrient intake
  - Circadian rhythm
  - Hormones
  - Gender
  - Race/ethnicity

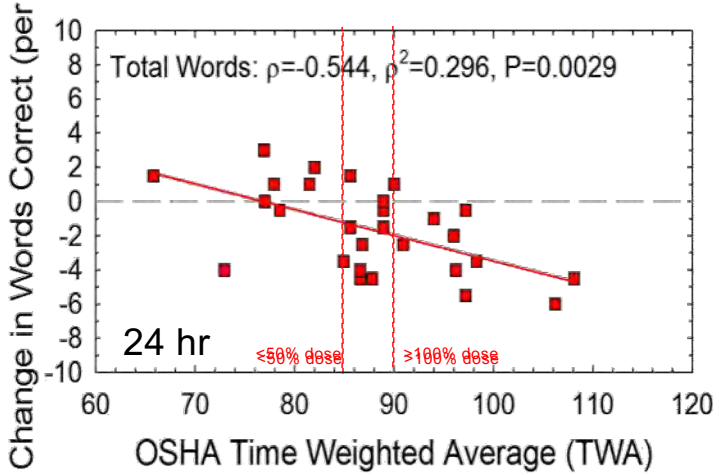

- Le Prell, C. G., Brewer, C., and Campbell, K.C.M. (2022). The audiogram: Detection of pure-tone stimuli in ototoxicity monitoring and assessments of investigational medicines for the inner ear. *Journal of the Acoustical Society of America, 151(1): 470-490, doi: 10.1121/10.0011739.*
- See various articles in JASA Special Issue: Noise-Induced Hearing Loss: Translating Risk from Animal Models to Real World Environments; https://asa.scitation.org/toc/jas/collection/10.1121/jas.2019.NIHLNS2019.issue-1

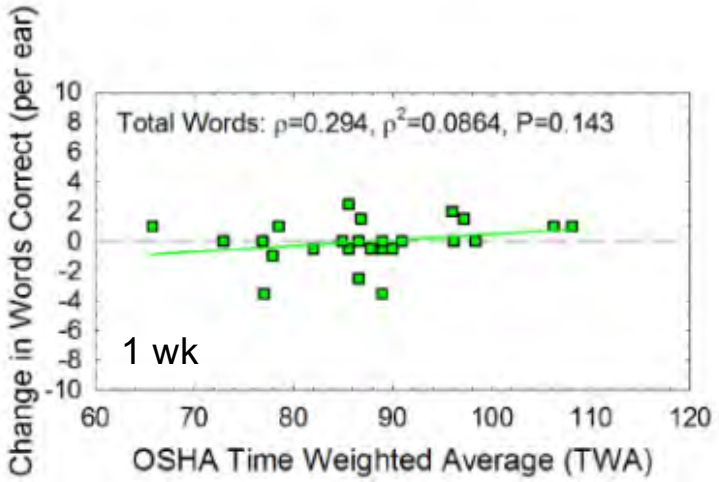
# How much exposure is safe for everyone?

- Reviews of NIHL in adults (Neitzel and Fligor, 2019) and children (Roberts and Neitzel, 2019) suggest:
  - exposure limit of **80 dB-A $L_{EX}$** ($L_{EX}$: 8-hour equivalent continuous average sound pressure level) would protect all but the most vulnerable individuals against NIHL
  - **75 dB-A $L_{EX}$** limit would be necessary if the goal were to completely prevent all NIHL even the most vulnerable individuals
- However:
- Data do not address whether risk for noise-induced tinnitus and hearing-in-noise deficits begin at same exposure level
- We do not yet have any way to identify who the most vulnerable individuals are in advance of noise injury


- Neit.zel RL, Fligor BJ. Risk of noise-induced hearing loss due to recreational sound: Review and recommendations. J Acoust Soc Am. 2019;146(5):3911-3921.
- Roberts B, Neitzel RL. Noise exposure limit for children in recreational settings: review of available evidence. J Acoust Soc Am. 2019;146(5):3922-3933

# Temporary hearing-in-noise deficits the day after exposure emerge at action level of 85 dBA TWA



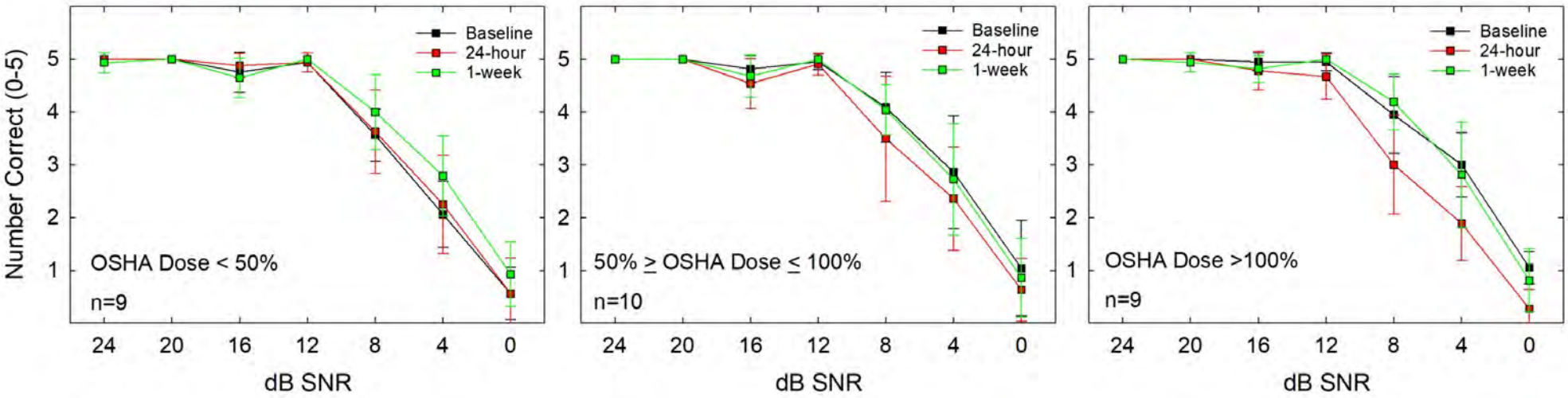




- 28 participants attended recreational event they deemed loud
  - Level: 93.3±7.8 dBA (range 73.1–104.2 dBA)
  - Duration: 4.2±3.5 hrs (range 1.5–16.0 hrs)
- Average dose and TWA calculated using 29 CFR 1910.95 (OSHA)
  - 168.4%±276% (range 3.5%–1,230.8%)
  - 87.8 dBA TWA±9.5 dBA (range 65.8–108.1 dBA TWA)
- No reliable threshold shift; dose-dependent hearing-in-noise shift that recovered within 1 week
- Marginally significant decrease in DPOAE amplitude at 24 hr but not 1 wk test
- No post-noise decrease in wave 1 amplitude



Adapted from Grinn, S., Baker, J., Wiseman, K., and Le Prell, C. G. Hidden hearing loss? No effect of common recreational noise exposure on cochlear nerve amplitude in humans. *Frontiers in Neuroscience, 11:465;* https://doi.org/10.3389/fnins.2017.00465 *CCBY*

# Temporary hearing-in-noise deficits evident in MOST difficult listening conditions




- Exposure Data:
  - < 50% OSHA dose (4 male, 5 female)
  - 50-100% OSHA dose (4 male, 6 female)
  - > 100% OSHA dose (3 male, 6 female)
- Average noise dose, calculated using 29 CFR 1910.95, was 168.4% ± 276% (range 3.5% – 1,230.8%)

Unpublished; supplemental analysis of data reported by Grinn, S., Baker, J., Wiseman, K., and Le Prell, C. G. Hidden hearing loss? No effect of common recreational noise exposure on cochlear nerve amplitude in humans. *Frontiers in Neuroscience, 11:465;* https://doi.org/10.3389/fnins.2017.00465

# Risks for OHC loss and synapse loss during occupational noise exposure difficult to determine

- Systematic review of ABR data from noise-exposed workers – 13 studies with ABR data from occupational noise-exposed populations
- Multiple reports that Wave I, III, and/or V latency was delayed
- Subset of studies that measured Wave I, III, or V amplitude reported smaller amplitudes
- The high prevalence of ABR waveform deficits across occupational noise groups contrasts with inconsistent deficits within leisure noise groups
- However, most noise-exposed worker cohorts had significant hearing loss – i.e., these were not “hidden” hearing losses
- Presence of NIHL suggests OHC pathology accompanied any neuropathic change that might potentially be inferred from the atypical ABR results

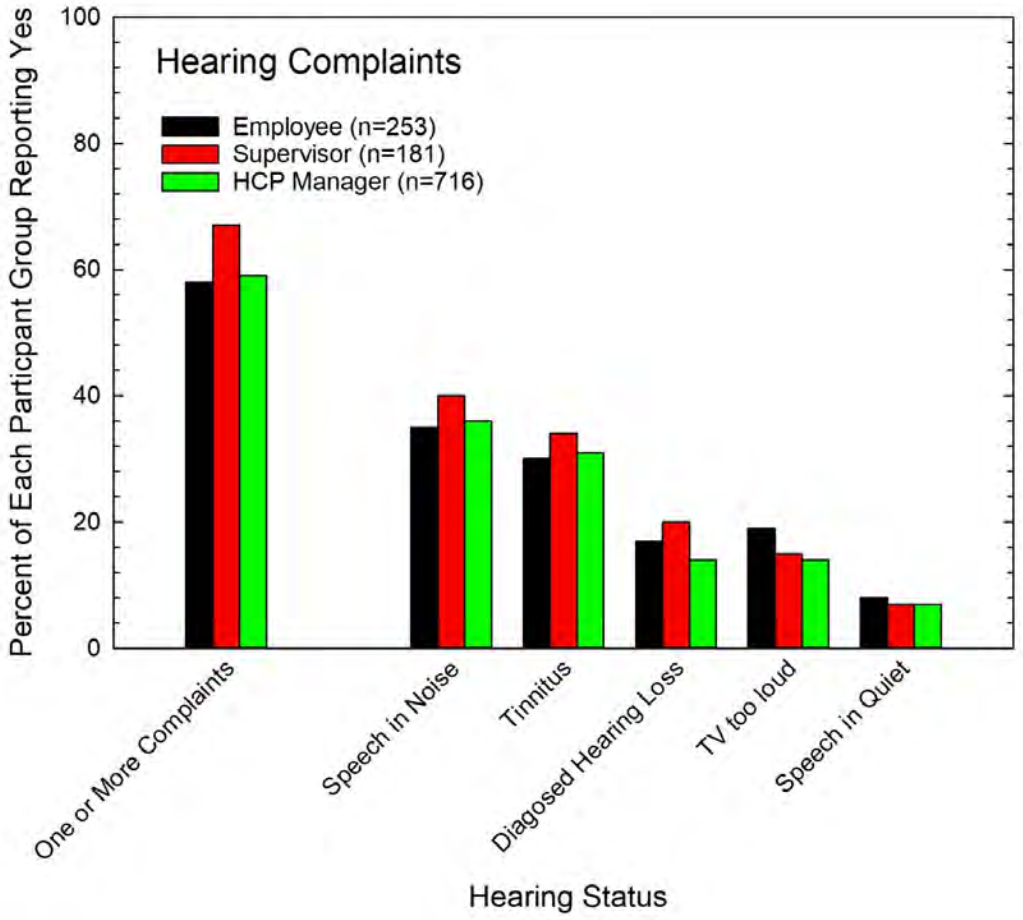


Le Prell, C. G. (2019). Effects of noise exposure on auditory brainstem response and speech-in-noise tasks: A review of the literature. *International Journal of Audiology*, *58*(sup1), S3-S32.

# High rate of hearing complaints with occupational noise

- Survey study recruiting workers required to wear HPDs, supervisors of workers who are required to wear HPD, and hearing conservation program managers
  - 60-65% reported ≥1 complaints
  - 35-40% reported hearing-in-noise issues
  - 30-35% reported tinnitus
  - 15-20% reported diagnosed hearing loss

**Tinnitus and hearing-in-noise difficulties were twice as common as diagnosed hearing loss; neither are monitored in occupational HCP's and there are no damage-risk criteria for these NIHD**




Jansen C, Cochran A, Fallon E, Le Prell CG. In preparation; presented at NHCA 2023.

# Audibility Needs

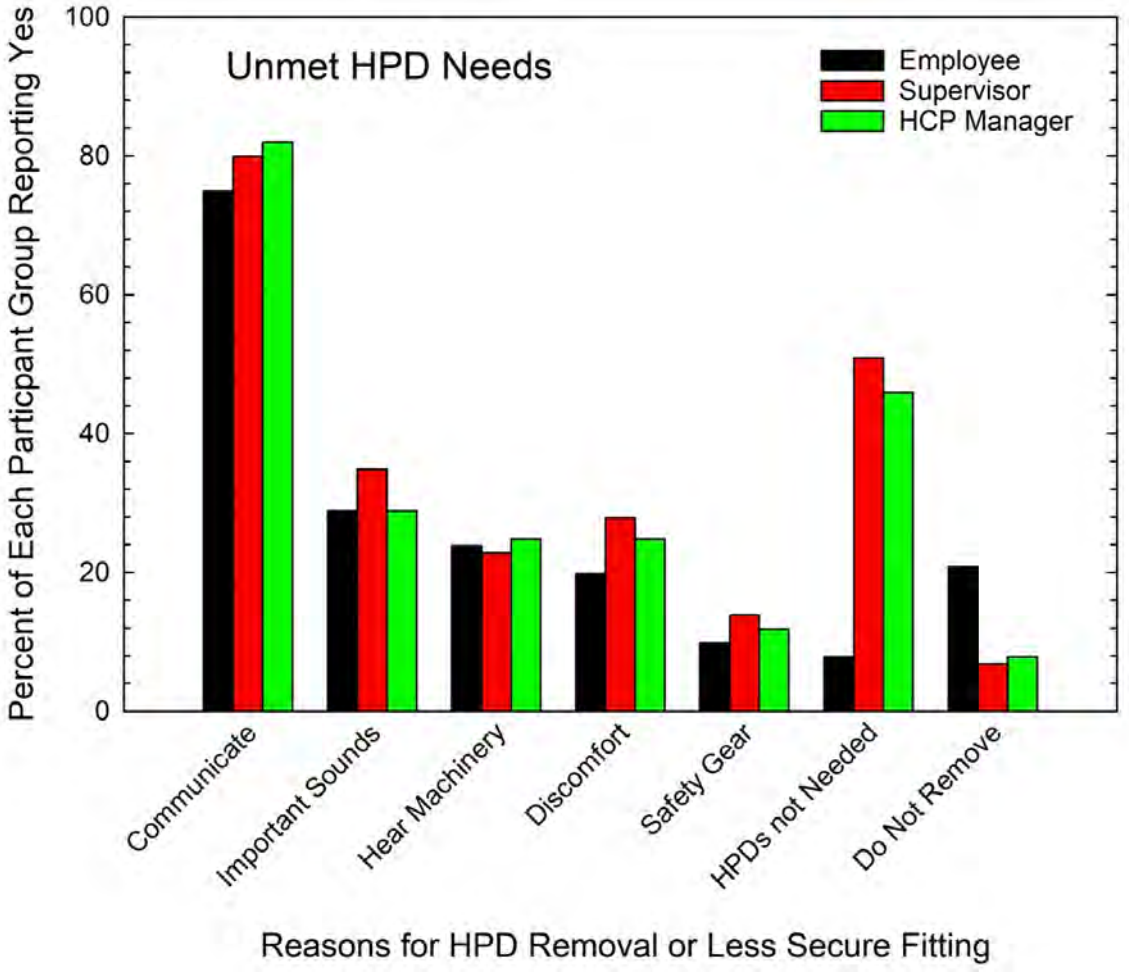
- **67% of Employee participants** reported sometimes removing HPDs to hear better while working
- **80% of Supervisor and 74% of HCP Manager participants** reported employees they supervise sometimes remove their HPDs to hear better while working

| Statement | Agreement Levels | Employee % (n=253) | Supervisor % (n=181) | HCP Managers % (n=718) |
|---|---|---|---|---|
| **I sometimes remove my hearing protectors to hear better while working.** | **Strongly Agree** | **16% (40)** | **21% (38)** | **14% (98)** |
| | **Agree** | **21% (54)** | **31% (56)** | **30% (213)** |
| | **Slightly Agree** | **30% (77)** | **28% (52)** | **30% (213)** |
| | Slightly Disagree | 5% (7) | 3% (6) | 9% (68) |
| | Disagree | 11% (28) | 11% (20) | 10% (71) |
| | Strongly Disagree | 17% (42) | 6% (11) | 7% (53) |

Jansen C, Cochran A, Fallon E, Le Prell CG. In preparation; presented at NHCA 2023.

# Reasons reported for removing or less securely fitting HPDs

- To communicate with co-workers – 75-80%
- Can't hear important sounds when wearing HPDs – 30-35%
- To hear machinery or processes better – 25%
- Not all reasons were audibility related
  - Discomfort – 20-30%
  - Don't work with other safety equipment – 10-15%




Jansen C, Cochran A, Fallon E, Le Prell CG. In preparation; presented at NHCA 2023.

# Suprathreshold deficits are major clinical concern regardless of whether synapse loss or OHC loss is cause

- Difficulties hearing in noise are one of most common complaints; can occur with or without hearing loss
- HLAA Voice of the Patient Report: 92% of responses included difficulty hearing in noise as a health concern; 82% of responses included difficulty hearing in noise as one of the top three most troublesome health concerns
- About 10% of patients seen for hearing-in-noise complaints with no audiometric loss at testing (Parthasarathy et al., 2020)
- Hearing-in-noise deficits are NOT diagnostic for synapse loss (although synapse loss might be inferred if OAEs are robust)


- Le Prell, C. G. (2019). Effects of noise exposure on auditory brainstem response and speech-in-noise tasks: A review of the literature. *International Journal of Audiology*, *58*(sup1), S3-S32.
- Parthasarathy A, Hancock KE, Bennett K, et al. Bottom-up and top-down neural signatures of disordered multi-talker speech perception in adults with normal hearing. eLife. 2020 Jan 21;9.
- HLAA Voice of the Patient Report, 2021

# Agenda

- Hidden hearing loss terms and definitions
- Noise-induced cochlear pathology
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- **Existing use of the audiogram, tinnitus surveys, hearing in noise tests, and ABR in clinical trials**
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# Clinical Trial Phases

- Phase 1: first in human, typically healthy volunteers, includes safety measures; typically small (20-30 participants)
- Phase 2: initial efforts to study efficacy in affected participant population; continued evaluation of safety; moderate sample sizes (~100, depending on desired power and other statistical considerations)
- Phase 3: large studies, often multi-site, used to determine benefits relevant to placebo control or standard of care (non-inferiority); large samples (could be several hundred to several thousand)



Bhowmik D, Chandira M, Maharajganj N, Pradesh U. (2010). Emerging trends of scope and opportunities Clinical trials in India. *International Journal of Pharmacy and Pharmaceutical Sciences.* 2(Suppl. 1):7-20.

# Key Definitions

- Outcome: measured variable
  - e.g., audiometric threshold, DPOAE amplitude
- Endpoint: analyzed parameter (e.g., change from baseline)
  - Primary endpoint – typically the most important outcome; addresses whether intervention prevents disease, or is better at preventing disease than standard therapy
  - Secondary endpoint – other relevant questions; can be mechanistic (e.g., a drug for osteoporosis could have fractures as primary endpoint could and improved bone density as secondary endpoint)
  - Multiple endpoints may be used when there is no consensus about which one will best serve the study goals, and an effect on any one will be sufficient evidence of effectiveness to support new drug indication
- Indication: use of a drug for treating a particular disease (e.g., use of a drug for NIHL prevention or ARHL treatment)


- Le Prell CG. 2021. Investigational medicinal products for the inner ear: Review of clinical trial characteristics in ClinicalTrials.gov. J Am Acad Audiol, 32(10):670–694.
- Le Prell, C. G. (2022). Prevention of noise-induced hearing loss using investigational medicines for the inner ear: previous trial outcomes should inform future trial design, Antioxid. Redox Signal., 36(16-18):1171-1202.

# Challenges in matching "HHL" endpoints to indications

- Per FDA: A therapeutic intervention may be said to confer clinical benefit **if it prolongs life, improves function, and/or improves the way a patient feels**
  - Changes in ABR amplitude (or other evoked potentials) may be earliest outcomes of disease or injury process; however, if there are no measurable perceptual deficits associated with those changes, clinical benefit and medical indication may be difficult to establish
  - Changes in audiogram are the most common clinical trial outcome but cochlear synaptopathy by definition does not affect the audiogram
  - Hearing-in-noise and tinnitus receiving significant discussion; ultimately up to FDA what constitutes clinically significant benefit

# Many possible outcome measures from which endpoints could be derived

- Tympanometry – status of tympanic membrane
- **Audiogram – pure-tone air-conduction thresholds**
  - **Speech reception threshold (SRT) – correlates well with PTA512**
- **Word recognition – identification of words in quiet**
- **Hearing-in-Noise – identification of words in sound background (babble, speech-shaped noise, etc.)**
- Otoacoustic Emissions – reflect health of outer hair cells, assuming normal conduction
  - Useful in diagnosis of auditory neuropathy (OAEs present, ABR reduced or absent)
- Electrocochleography (eCochG)/Auditory brainstem response (ABR) – reflect health of afferent neural pathway, assuming normal conduction and intact outer hair cells
  - Useful in diagnosis of auditory neuropathy (OAEs present, ABR reduced or absent)
- **Tinnitus surveys, Hearing handicap surveys, other surveys?**

# U.S. Hearing Loss Prevention Clinical Trial Summary

- Data collected from clinicaltrials.gov
  - 9 clinical trials evaluating NIHL otoprotection
  - 30 clinical trials evaluating DIHL otoprotection
  - 9 clinical trials evaluating therapeutics for acute SSNHL
  - 11 clinical trials evaluating drug benefits in patients with stable SNHL, including ARHL
- Some trials terminated early
- Some trials do not have results posted
- Some trials did not meet study endpoints

Le Prell CG. 2021. Investigational medicinal products for the inner ear: Review of clinical trial characteristics in ClinicalTrials.gov. J Am Acad Audiol, 32(10):670–694.

# Method of drug delivery varies across indications in hearing loss prevention trials posted on ClinicalTrials.gov

| Method of Drug Delivery | NIHL (n = 9) | DIHL (n = 30) | Acute SSNHL (n = 9) | SNHL (n = 13) |
|---|---|---|---|---|
| Oral | 9; 100% | 9; 30% | 2; 22% | 5; 38% |
| Intra-tympanic/ eardrop | 0 | 11; 37% | 6; 67% | 6; 46% |
| Intra-venous | 0 | 10; 33% | 1; 11% | 0 |
| Sub-cutaneous | 0 | 0 | 0 | 2; 15% |

For detailed list of which drugs were administered for each indication, see Le Prell CG. 2021. Investigational medicinal products for the inner ear: Review of clinical trial characteristics in ClinicalTrials.gov. J Am Acad Audiol, 32(10):670–694.

# Some drugs administered in multiple ways

## Oral drug delivery

- Alpha-lipoic acid
- Aspirin
- AUT00063
- Dexamethasone
- D-methionine
- Vitamins A, C, E plus magnesium
- Fludrocortisone
- EPI-743/ Vincerinone

## Intra-tympanic injection

- AM-111
- Dexamethasone
- FX-322
- Methylprednisolone
- N-acetylcysteine
- OTO-413/BDNF
- PIPE-505
- Sodium thiosulfate
- STR001-IT
- Ginkgo biloba
- Huperzine A
- Methylprednisolone
- N-acetylcysteine
- PF-04958242
- SENS-401
- SPI-1005/Ebselen
- Zinc gluconate
- Zonisamide



Le Prell CG. 2021. Investigational medicinal products for the inner ear: Review of clinical trial characteristics in ClinicalTrials.gov. J Am Acad Audiol, 32(10):670–694.

# Audiogram is most common endpoint measure in hearing loss prevention trials posted on ClinicalTrials.gov

| Primary, Secondary, or Other Endpoint | NIHL (n = 9) | DIHL (n = 30) | Acute SSNHL (n = 9) | SNHL (n = 13) |
|---|---|---|---|---|
| Threshold Shift | 7; 78% | 14; 47% | 9; 100% | 8; 62% |
| Rate of ASHA SOC | 0 | 6; 20% | 0 | 0 |
| Rate of CTCAE | 0 | 3; 10% | 0 | 0 |
| Rate of Brock | 0 | 1; 3% | 0 | 0 |
| Rate of Boston SIOP | 0 | 1; 3% | 0 | 0 |
| Rate of Tune | 0 | 1; 3% | 0 | 0 |
| Other STS Rate | 1; 11% | 8; 27% | 0 | 1; 8% |



Le Prell CG. 2021. Investigational medicinal products for the inner ear: Review of clinical trial characteristics in ClinicalTrials.gov. J Am Acad Audiol, 32(10):670–694.

# Other endpoint measures rarely used in hearing loss prevention trials posted on ClinicalTrials.gov

| Primary, Secondary, or Other Endpoint | NIHL (n = 9) | DIHL (n = 30) | Acute SSNHL (n = 9) | SNHL (n = 13) |
|---|---|---|---|---|
| DPOAE shift | 5;56% | 10; 33% | 0 | 1; 8% |
| EHF Threshold shift | 1; 11% | 5; 17% | 0 | 2; 15% |
| Word Recognition Change | 0 | 2; 7% | 4; 44% | 6; 46% |
| **Hearing in Noise Change** | **2; 22%** | **2; 7%** | **0** | **5; 38%** |
| **Change in Tinnitus** | **5; 56%** | **7; 23%** | **1;11%** | **5; 38%** |
| **ABR Amplitude Shift** | **0** | **0** | **0** | **2; 15%** |

Le Prell CG. 2021. Investigational medicinal products for the inner ear: Review of clinical trial characteristics in ClinicalTrials.gov. J Am Acad Audiol, 32(10):670–694.

# Primary/Co-Primary endpoints in NIHL prevention studies published in scientific literature (n=24) or posted on ClinicalTrials.gov (n=7)

| | PTS (pre-Tx) (n = 4 trials) | PTS (Post-tx) (n = 5 trials) | TTS (pre-tx) (n = 20 trials) | TTS (post-tx) (n = 2 trials) | Total (n = 31 trials) |
|---|---|---|---|---|---|
| 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% |
| Rate of 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 change | 0 | 0 | 4/20; 20% | 0 | 4/31; 13% |
| TEOAE amplitude change | 0 | 0 | 1/20; 5% | 0 | 1/31; 3% |
| Word recognition change ≥15% | 0 | 1/5; 20% | 0 | 0 | 1/31; 3% |

Le Prell, C. G. (2022). Prevention of noise-induced hearing loss using investigational medicines for the inner ear: previous trial outcomes should inform future trial design, Antioxid. Redox Signal., 36(16-18):1171-1202.

# DPOAE, ECochG, Hearing-in-noise as secondary outcome measures in NIHL prevention studies published in scientific literature (n=24) or posted on ClinicalTrials.gov (n=7)

| | PTS pretreatment (n = 4 trials) | PTS post-treatment (n = 5 trials) | TTS pretreatment (n = 20 trials) | TTS post-treatment (n = 2 trials) | Total (n = 31 trials) |
|---|---|---|---|---|---|
| DPOAE amplitude shift | 2/4; 50% | 2/5; 40% | 3/20; 15% | 0 | 7/31; 23% |
| DPOAE threshold shift | 0 | 0 | 1/20; 5% | 0 | 1/31; 3% |
| DPOAE unspecified shift | 0 | 0 | 1/20; 5% | 0 | 1/31; 3% |
| TEOAE amplitude shift | 0 | 0 | 1/20; 5% | 1/1; 100% | 2/31; 6% |
| CAP/ECochG amplitude shift | 1/4; 25% | 2/5; 40% | 1/20; 5% | 0 | 4/31; 13% |
| Change in Hearing-in-Noise | 1/4; 25% | 2/5; 40% | 1/20; 5% | 0 | 4/31; 13% |

Le Prell, C. G. (2022). Prevention of noise-induced hearing loss using investigational medicines for the inner ear: previous trial outcomes should inform future trial design, Antioxid. Redox Signal., 36(16-18):1171-1202.

# Tinnitus Trials are Not Standardized Either

- Review of 66 clinical trials by Jin and Tyler revealed assortment of outcomes
- Scaling methods were the most common (37 studies)
- Questionnaires also commonly used
  - Tinnitus Handicap Inventory used in 27 studies
  - Tinnitus Functional Index used in 13 studies
  - Tinnitus Handicap Questionnaire used in 5 studies
- Patient self-report used in 19 studies
- Loudness (10), pitch (5), minimal masking level (4) less commonly measured
- fMRI used as an objective measure in 2 studies



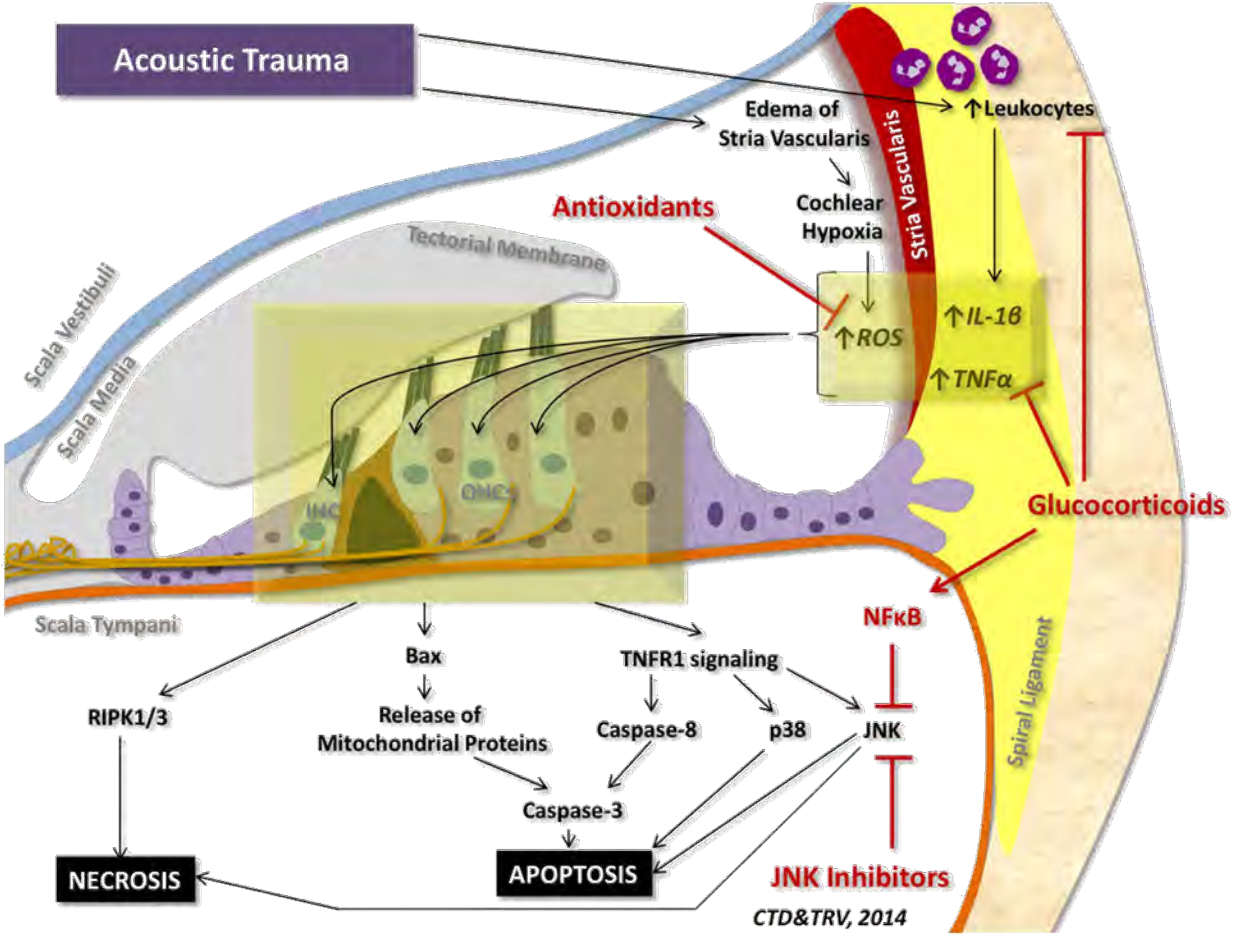
Jin, I.-K. and Tyler, R. S. (2022). Measuring tinnitus in pharmaceutical clinical trials. The Journal of the Acoustical Society of America 152, 3843-3849; doi: 10.1121/10.0014699

# Agenda

- Hidden hearing loss terms and definitions
- Noise-induced cochlear pathology
- Some points of agreement on cochlear synaptopathy, and some open questions
- Existing use of the audiogram, tinnitus surveys, hearing in noise tests, and ABR in clinical trials
- **Investigational medicines for hearing loss prevention and hearing restoration**

# Most but not all efforts focus on OHC protection

- **Antioxidants** reduce ROS, RNS, so they can be safely excreted (ebselen, D-Met, NAC, dietary antioxidants)
- **Glucocorticoids** reduce inflammation driven by TNFα and NFκB
- **JNK inhibitors** block "death receptor" activation
- **Gene therapy** is different; drives development of new cells




Dinh, C. T., Goncalves, S., Bas, E., Van De Water, T. R., & Zine, A. (2015). Molecular regulation of auditory hair cell death and approaches to protect sensory receptor cells and/or stimulate repair following acoustic trauma. Frontiers in Cellular Neuroscience, 9, 96. https://doi.org/10.3389/fncel.2015.00096; CC BY

# Significant Commercial Development Activity

June 2018 search to identify companies working in the field of therapeutics for inner ear and central hearing disorders

43 companies with pre-clinical or clinical research programs identified

- 24 in United States, 4 in France, 4 in Germany, 3 in Switzerland, 2 in the United Kingdom, 1 each in Japan, Israel, Sweden, Denmark, Belgium and the Netherlands

- **Otoprotection**
  - **24 companies, 37 therapeutic programs**
  - **Ototoxicity, noise injury, aging, ISSNHL, CI insertion trauma**
  - **20 programs preclinical, 4 Phase I programs, 5 Phase 2 programs (2 failed), 3 Phase 3 programs**
- Regeneration
  - 15 companies, 16 therapeutic programs
  - 13 programs pre-clinical, 2 Phase I programs, 1 Phase I/2 program
- Tinnitus Reduction
  - 12 companies, 13 therapeutic programs
  - 8 programs preclinical, 2 Phase I programs, 1 Phase 2 (failed), 2 Phase 3 programs (failed)
- Central Hearing Disorders
  - 1 company, 1 therapeutic program
  - Preclinical
- Balance
  - 5 companies, 5 therapeutic programs
  - 2 programs preclinical, 1 Phase I programs, 1 Phase 2 programs, 1 Phase 3 programs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- For additional review and discussion see Le Prell CG (2023): Preclinical prospects of investigational agents for hearing loss treatment, Expert Opinion on Investigational Drugs, 32(8):685-692

# First drug for a hearing loss prevention indication approved

- **On September 20, 2022, the US Food and Drug Administration approved sodium thiosulfate (Pedmark, Fennec Pharmaceuticals Inc.) to reduce the risk of ototoxicity associated with cisplatin in pediatric patients 1 month and older with localized, non-metastatic solid tumors**
- **On June 6, 2023, the European Commission approved Pedmarqsi™ for use in all 27 European Member states plus Iceland, Norway, and Lichtenstein.**
- Efficacy evaluated in two multicenter open-label, randomized controlled trials in pediatric patients undergoing treatment with cisplatin-based chemotherapy for cancer: SIOPEL 6 (NCT00652132) and COG ACCL0431 (NCT00716976)
- Incidence of hearing loss was lower in sodium thiosulfate/cisplatin arm (44%) relative to cisplatin-alone arm (58%)
- Most common adverse events in the 2 trials were vomiting, nausea, decreased hemoglobin, hypernatremia (high sodium levels in blood), and hypokalemia (low potassium levels in blood)

Dhillon, S. (2023). Sodium thiosulfate: Pediatric first approval. *Paediatr Drugs*, *25*(2), 239-244.

# Investigational therapies for cochlear synaptopathy

- Neurotrophic factors are of high interest for synaptic regeneration
- Animal data suggest restored synapses and restored wave I amplitude with neurotrophic factor administration (see work from Corfas lab)
- Evidence of post-noise synaptic repair in some but not all rodent species, in absence of drug therapies
- Questions remain – What is most appropriate model for human? What is the clinical correlate of synapse loss in humans? How should clinical trials be designed in face of uncertainties related to pathology and function?


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# Guidance for patients

- There are no drugs approved for prevention of NIHL
- Level of evidence for dietary supplement benefit is low
- But NIHL is preventable with known tools
  - Decreasing exposure level and/or exposure duration is the most effective
  - Hearing protection devices (earplugs, earmuffs) are effective when used consistently and correctly
- HPD options are diverse: uniform-attenuation (musicians) HPDs, electronic HPDs, custom HPDs, are all options that should be offered to patients as appropriate for their needs

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# Questions and Discussion

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