PHARMACEUTICAL INTERVENTIONS FOR HEARING LOSS (PIHL)
Newsletter – Winter 2019/Edition 8

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AN INTRODUCTION TO PHARMACEUTICAL INTERVENTIONS FOR HEARING LOSS: NOISE COMMITTEE

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The Department of Defense (DoD) Hearing Center of Excellence (HCE) was legislated by Congress in the 2009 National Defense Authorization Act. The HCE is focused on the prevention, diagnosis, mitigation, treatment, and rehabilitation of hearing loss and auditory injury, and it includes partnerships with the Department of Veterans Affairs, or VA, institutions of higher education, and other mission-minded public and private organizations. The mission of the DoD HCE is to optimize operational effectiveness, heighten medical readiness, and enhance quality of life through collaborative leadership and advocacy for hearing and balance health initiatives. Towards this end, the HCE has sponsored several open-access supplemental journal issues to promote knowledge and research in the overall area of Pharmaceutical Interventions for Hearing Loss (PIHL), managed by working groups under the umbrella of the DoD HCE PIHL committee. These high-impact series of manuscripts have been published over the past several years (Otology and Neurotology, 2016; Hearing Research, 2017; Frontiers in Cellular Neuroscience, 2018; International Journal of Audiology, in press).

The abstracts published here are brief introductions to the next series of articles, which have been solicited from working group members and other experts in the field. These articles are intended to highlight challenges related to pre-clinical testing of potential otoprotective drug agents, and their translation to human clinical trials. Otoprotective drugs will ultimately be developed for and targeted to specific populations and markets, but right now, there is only limited understanding of who the at-risk populations are. Unfortunately, animal models have not been characterized in enough detail to allow the selection of the most appropriate pre-clinical test models for many of the populations that might be of interest for potential interventions. All of the invited submissions were selected with this translational framework in mind.

The overarching goal of the current series is to 1) provide insight into the populations for whom pharmaceutical interventions might, or might not, be appropriate, 2) highlight the factors that drive the significant individual variability

observed in humans and the difficulties these create for translation from animal models into clinical trials and eventually use by specific patient populations, and 3) review the animal models that have been used, in particular highlighting the relevance to the human populations of interest.

The articles contained in this series of papers are organized so as to describe the real-world noise hazards and patterns of injury (Section 1) in as much detail as possible, and provide explanations of sources of variability (Section 2), so that the most appropriate animal model can be selected (Section 3) when a drug is developed for potential application.

Medicines discovery for auditory disease: Challenges for industry

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Discovery of transformative medicines involves thousands of individuals from the seed of an idea to the final pills in the box in the patient's hand, so collaborations engaging wide multi-disciplinary expertise are key to future innovations, particularly in uncharted therapeutic areas such as hearing loss.[1] Entry into new therapeutic indications requires a high degree of confidence in the insights around human biology, the translational understanding and the patient needs to encourage the level of investment required to translate basic science into a medicine of value.

An analysis of ten years R&D activity found the likelihood of achieving approval upon entering Phase 1 was on average about 10%.[2] Most relevant to the diseases of the inner ear is that historically neuroscience indications are amongst those with the lowest Probability of Success (PoS), and many large pharma companies have strategically decided to discontinue activity in neuroscience. Further analysis revealed that where Phase II (PhII) studies had completed and failed, often the data were not available to make informed decisions as to whether the biological mechanism of the drug entity taken into the clinic had been fully tested or not. An analysis published by scientists from Pfizer highlighted that in 43% of failed PhII studies, an informed decision on the target could not be made.[3] The Three Pillars of Survival were derived from their analysis, where if all three criteria were met then it would possible to make an informed decision and overall improve the PoS. [3]

Across the pharmaceutical industry these learnings, insights and criteria were applied with rigour and discipline to improve decision making and PoS, so

that the exposure of the drug at the target site of action over the desired period time was understood, that there was evidence of target engagement and that the pharmacology and pharmacodynamic effects observed were consistent with pharmacokinetic data.[4, 5] This led to preclinical evaluation requiring these types of data to be routinely collected and rigorous analysis be applied to increase confidence in predicting potential human doses, exposures and efficacy. For some therapeutic areas, such as neuroscience and hearing loss, accessing all these types of data is very challenging and requires innovative solutions or embracing the risk without these attendant data. Through focusing on the three cornerstones of medicine discovery biological target, molecular entity and clinical studies with a range of initiatives the drug discovery industry has reported encouraging signs and evidence of improvement in productivity have been claimed.[6]

The unmet need for effective treatments for inner ear and auditory disorders is recognised, as there are no licensed drug treatments, and devices are not able to restore full hearing. Drug discovery activity is focused on sensorineural dysfunctions, where the different underlying pathologies will drive the observed hearing loss.[7] Nonetheless hearing loss patient populations may be broken down into three groups with differing putative pathologies that impact on hearing: presbycusis (age related hearing loss), noise induced hearing loss (NIHL), and ototoxicity. Using the knowledge of some of the possible pathologies driving auditory dysfunction, three therapeutic strategies are suggested: otoprotection, restoration of hearing, and reduction of tinnitus symptoms.

Preventing hearing loss in patients who will be exposed to ototoxic agents makes for an attractive focused drug discovery opportunity. It is probable that these patients may only require a short dosing regimen, lessening the safety challenges that arise with chronic treatments. This presents an opportunity for developing and establishing translational understanding, and may provide a platform to address additional hearing loss patient groups. The growing presbycusis patient population presents with many different underlying pathologies, and diagnosis of these specific pathologies will be essential to align the right medicine to the right patient.[8, 9] Preclinically, the disease relevance of animal models needs to be understood, including how each model specifically relates to human hearing disorders.[10] The likely requirement of chronic treatment to delay or prevent progressive hearing loss will require the appropriate safety profile that a non-life-threatening condition demands.

Restoration of hearing with a regenerative strategy is attractive to patients, physicians, payers and pharma, as the clear benefit may well be immediate and can be easily demonstrated as compared to a reduction in the slow decline of hearing in the ageing presbycusis population. Biological strategies beyond sensory hair cell regeneration must be pursued, as other structures within the inner ear are essential and vulnerable.[7] The early science and hope within this space is developing rapidly, but the clinical translational understanding is currently undeveloped, and the relevance of in vivo animal models to human disease needs to be established.[11, 12] Ensuring safety with short acute dosing regimens is easier to achieve than those requiring chronic treatments. Local topical delivery into the inner ear would reduce systemic exposure and associated safety risk, and may be acceptable for short limited dosing regimens, where clear efficacy was achieved. [13, 14] It is exactly this element that encourages target strategies using gene vector or gene editing platforms, and further investment in these modalities for hearing loss can be expected.[15, 16]

Specific niche indications will provide opportunity to bring forward treatments and increase confidence of the translational understanding of the field. However, access to broader patient populations with generalised hearing loss requires improved biological insights. Future innovation and collaboration will be essential, and key areas that require attention include:

- Greater understanding of physiologically relevant biological targets and genetics.
- Understanding the role of the immune system and inflammation.
- Standardisation of preclinical models and insights into their translational relevance.
- Utilise human and/or patient derived tissue preclinically to increase confidence in biology of interest Improved diagnostics to select the most appropriate patients for specific therapies.
- Establishment of inner ear delivery technologies and methodology to measure drug concentrations and target engagement.
- Engagement with patients, physicians, regulators and payers to better understand & align clinical studies with desired outcomes.
- Maximisation of the limited resources across the community.

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ABSTRACTS FOR JASA SPECIAL ISSUE:

Section 1: Human Exposures and Associated Hearing Loss Profiles: Who are the Target Populations that Drugs Intended to Prevent NIHL Might Benefit?

Characterization of Acute Changes in Hearing among Military Populations

Quintin Hecht & Tanisha Hammill

Noise induced hearing loss and tinnitus continue to be the most prevalent service-connected disabilities experienced by Veterans of military service in the United States (Veteran Benefits Administration, 2016), and recent research suggests hearing impairment can have significant negative impacts on the readiness and combat effectiveness of active duty military personnel (Sheffield et al, 2016; Brungart, 2014; Peters and Garinther, 1990). Furthermore, there is now evidence that listeners may be experiencing long-term damage (synaptopathy or "hidden hearing loss") from noise exposures that cause temporary, rather than permanent, shifts in hearing thresholds (Liberman et al., 2016). Temporary threshold shifts (TTS) can be caused by noise exposure, and repeated exposures or extreme noise exposure can cause a permanent threshold shift (PTS); while TTS appears to be associated with edema, metabolic fatigue and biochemical reactions, PTS follows structural changes to the hair cells or even complete loss of outer hair cells, detachment of portions of the organ of corti, and other mechanical damage (Clifford et al, 2009; St Onge et al, 2011; Cho et al, 2013; Okpala, 2011). TTS generally recovers within hours or days, and repeated exposures precipitate PTS (St Onge et al, 2011; Okpala, 2011; Nakashima et al, 2015). Despite this knowledge, the current gold-standard metric of noise-induced hearing damage in the military is an annual air-conduction audiogram which is often not administered at the time of an acoustic injury, but rather upon the anniversary date of the individual assignment within their unit and hearing conservation program. By the time an individual is seen for their annual hearing test he/she may have already experienced numerous TTSs or even a PTS, thus losing the window of opportunity to identify the hazard and apply preventative measures, to include targeted education, increased hearing protection devices (HPDs) strategies, or even future pharmaceuticals interventions.

Steady state noise causes hearing loss gradually as the time-weighted average noise exposure exceeds safe levels, while blast exposure can cause immediate and sometimes permanent damage. Aircraft and military vehicles

can be as loud as 110-150 dB, yet a blast from an improvised explosive device (IED) is estimated to reach 180 dB (Wells et al, 2015; Rajguru, 2013). Blast-related injury causes a diverse constellation of otologic concerns and audiometric patterns. Patients present with tympanic membrane perforations, conductive hearing losses, sensorineural hearing loss, mixed hearing loss, dizziness, and tinnitus (Remenschneider et al, 2014; Dougherty et al, 2013; Joseph et al, 2016; Helfer et al, 2011; Pusz and Robitschek, 2017). This evidence highlights the fact that repeated exposures, long-term exposures, and single-event blasts can cause significant auditory damage. Military members can be exposed to hazardous noise exposure (steady state or blast/impulse) during their everyday jobs, training events, and deployments, yet not all of these individuals receive serial audiological monitoring and those that do often do not have their hearing assessed at the time of auditory damage. Many weapons, vehicles, ships, and aircraft produce hazardous noise as a result of the energy released to produce their objectives (power, speed, lethality). In many cases, noise controls cannot be applied without decreasing mission effectiveness, leaving hearing protection devices (HPDs) as the only line of defense to noise damage.

The dose-response relationship and mechanisms behind noise-induced hearing loss (NIHL) are still not fully understood. Many military operations cannot fully abate noise hazards without decreasing mission success, and the effects of this truth have contributed to countless hearing loss and tinnitus diagnoses and Veterans Affairs (VA) compensation claims. The need to understand auditory injury and develop pharmaceutical interventions (both prophylactic and rescue agent) is paramount now more than ever. Therefore, the DoD has developed a study to Characterize Acute or Short-term acquired Military Population Auditory Shifts (CHASMPAS) to characterize potentially hazardous noise exposures experienced by specific subgroups in the military population and identify any changes in hearing that might be caused by those exposures. In addition to revealing targets for additional preventative strategies such as hearing conservation education or higher HPD protections, data from this study will also aid in the identification of populations suitable to receive novel otoprotectant or otorescue pharmaceuticals.

It is anticipated that the results of this study will identify populations that would be most likely to obtain measurable benefit from enhanced prevention strategies, including the use of pharmaceuticals either prophylactically or as a rescue agent. Also, it is expected that this study will: yield data to support refinement of acoustic injury standards, develop improved methods for monitoring small changes in the hearing of at-risk populations, develop a better

understanding of the dose-response relationship between noise/blast exposure and changes in hearing performance, and identify risk factors that may increase the likelihood of hearing injury from noise and blast exposure.

Excessive noise exposure is a long-known but poorly characterized risk to military populations. As technologies advance in HPDs and pharmaceutical interventions for hearing loss, it is increasingly vital to have detailed information about the hazards and outcomes present in military training and operational environments in order to optimize and personalize protection strategies for the warfighter. Noise exposures and their auditory functional impacts determined by the CHASMPAS study will be used to develop novel preventative strategies for Service members exposed to hazardous noise.

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Noise exposure and protection model for outdoor shooting ranges[1]

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Permanent hearing loss among US military personnel following basic training with ballistic weapons shooting has been documented to be about 13%.[1] Anecdotal evidence also suggests that hearing loss among military shooting range instructors may be common. Hearing loss could likely be reduced through increased compliance with hearing protection measures that achieve noise exposure daily limits.[2] However, an assessment of compliance requires knowledge of the noise levels to which instructors and trainees are exposed during shooting range exercises.

A model of noise exposure on shooting ranges is desired for the prediction and assessment of hearing protection measures to reduce the risk of hearing damage. A custom hearing protection calculator is being developed by the Air Force Research Laboratory in conjunction with Brigham Young University and the Centers for Disease Control and Prevention. The model for this calculator estimates the 8-hour time-weighted average (TWA) A-weighted noise levels**Error! Bookmark not defined.** for all shooters lined up in a training scenario and the instructors in the area behind the firing line.

The noise model is being developed and tested using data collected from an M16A4 military rifle, but will be expanded later to include multiple weapons. With funding from the Office of Naval Research, extensive measurements were made of an M16A4 at the Weapons Training Battalion (WTB) at Quantico, VA, in 2017.[3] Over 100 microphones were set up for this experiment, with the closest microphones 1 m from the weapon, and the farthest 75 m away. With the microphones in place, US Marine personnel fired the weapon in multiple configurations including while standing, kneeling, and prone. Measurements were made with only one person (the shooter) in the range area, as well as a more operationally relevant scenario with multiple shooters standing along the firing line. In addition, a special measurement was made where the shooter himself was removed and replaced by a weapon test stand with the M16A4 mounted and fired from a distance by a tether, and two microphones placed where the shooter's ears would have been. This was done to investigate the sound field created by the weapon without the influence of the shooter's

head/body to interfere. All data were collected in accordance with national[4] and DoD[5] standards for impulsive sound sources.

The technical details of the creation and validation of the exposure model will appear[6] in a special issue of the Journal of the Acoustical Society of America, hosted by the HCE. Two key findings are shown in the article. 1) The model is validated against a real-world shooting exercise, with 13 shooters in a lineup firing multiple rounds each. Using this benchmark, the model is shown to be accurate to within 2-3 dB. 2) The highest exposure to a shooter on an outdoor range by far comes from his own weapon, with the sum of all other weapons in the lineup adding only 3-4 dB to his total exposure (assuming 3-m spacing between shooting lanes).

An example of 8-hour TWA noise exposures for a multi-shooter exercise is shown in Figure 1. [Note that the 8-hour TWA is the same as the 8-hour A-weighted equivalent level (L_{Aeq8hr}) when a 3-dB-per-doubling exchange rate (i.e. the equal energy hypothesis) is used.] The example is comprised of 13 shooters (marked by squares) in adjacent lanes spaced 3 m apart along a lineup, firing 10 rounds each. The direction of fire is shown as "up" Figure 1. This may or may not represent a realistic training exercise, and no hearing protection attenuations have yet been applied. The yellow region shows that the highest noise levels are in front of the firing line, with levels decreasing with distance behind the line. The shooters in the lineup and instructors standing very close will receive the highest noise exposures, but noise levels as far back as 10 m or more can still be significant.

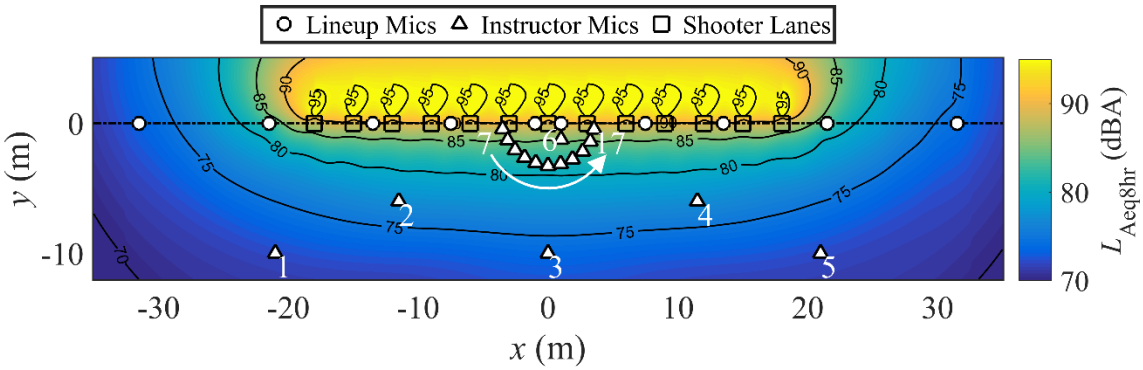

Figure 1 Noise exposure map for a theoretical shooting range training scenario.

The application of this model to real-world training scenarios will be presented at the 6th Workshop on Battlefield Acoustics in 2018.[7] The briefing will include discussion of total attenuated noise exposures for trainees and instructors wearing various hearing protection devices. The versatility and usefulness of the exposure model will be demonstrated with a focus on operationally relevant outcomes.

The 2017 WTB dataset for the M16A4 is more extensive than typical noise measurements for ballistic weaponry. It represents rich opportunities for further development of noise exposure measurement and modeling. Future work will include:

- Creation of user-friendly custom exposure calculator software.
- Database expansion to include noise models for a wide array of military weapons, including small arms (pistols, rifles, and shotguns) and larger weapons (explosive charges, mortars, rocket-launched arms, and large-caliber ballistics).
- Models for use in covered ranges, indoor ranges, combat spaces, and other operational environments.
- Comparison of weapons measurements made in controlled studies without the presence of personnel**Error! Bookmark not defined.**,[8] to personal monitoring (body-worn)[9] devices used for personal dosimetry applications.

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report are those of the authors and do not represent any official policy of the Centers for Disease Control and Prevention or the National Institute for Occupational Safety and Health. Mention of company names and products does not constitute endorsement by the CDC or NIOSH.

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Exposure to Noise via Tanks, Planes, and Ships: Patterns of Exposure and Potential Contributions to Hearing Loss

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Experience of Soldiers in service to our country is going to include exposure to loud sounds. In fact, that experience is going to include exposure to some of the most intense sounds that can be found in any occupation. For example, with the exception of the bayonet and the crossbow (which are used today by our Special Forces) every weapon system makes more than 140 dBP, the threshold of safe exposure for impulse noise, at the operator's ears. Several whole classes of weapon systems expose crew to levels that exceed 180 dBP. Almost all of the transportation platforms expose crew and passengers to more than 85 dBA while operating, which is the threshold of safe exposure for steady-state (continuous) noise. In fact, several cause exposures greater than 110 dBA.

Uniquely, the Army explicitly follows a policy of "train as you fight." This means our Soldiers are exposed to the same intense sounds during training missions as they would be in battle. In either case the severity of the exposures carries with it potentially serious consequences to Soldier health. Great reliance is placed on use of personal protective equipment to mitigate against the loud levels.

Weapon System Noise: Small Arms

Not all Soldiering occupations involve routine exposure to gunfire. However, all Soldiers are required to at least demonstrate proficiency in small arms weapon use every year. Therefore, all Soldiers are annually exposed to hazardous levels of impulse noise. For this reason, all Soldiers have their hearing acuity checked at least annually, to make sure they are properly using their provided hearing protection when using their small arms weapons, and to receive refresher training on various aspects of hearing readiness and conservation. Small arms weapons use ammunition that come in a variety of sizes, or calibers, and these cartridges each have a casing housing the propellant that drives the bullet, or front part of the cartridge assembly, from the gun. The amount of propellant in the cartridges largely determines how much noise is generated when the weapon is fired. When detonated, the exploding propellant causes a pressure spike to travel down the barrel of the gun, which becomes an expanding shock wave when it leaves the muzzle causing the impulse noise we associate with gunfire. This muzzle blast does not propagate uniformly in all directions. Most of its energy is directed downrange, with lesser amounts travelling to the sides and rear. For that reason, a Solder on the firing

line at a range may actually get exposed to more noise when next to a gun being fired than does the shooter of that gun.

Typical small arms systems cause the shooter to be exposed to sound in the low-to mid-150 dBP range, and adjacent shooters to be exposed to sounds some 8 to 10 dB higher. Exact levels depend on how far the muzzle is from the shooter (some guns can be fitted with more than one length barrel), and particularly on which attachments are fit to the muzzle. If the muzzle has a flash or sound-suppressor (silencer) on it, pressure levels can be reduced by 10 to 15 dB or more. On the other hand, if the muzzle has a muzzle brake on it (to minimize recoil) much of the energy that had been going downrange gets redirected back towards the shooter, increasing exposure levels significantly, by 15 to 20 dB or so.

The hazard associated with the impulse sound is that it may physically damage the delicate nerve tissues in the inner ear, in addition to causing the kinds of metabolic changes normally associated with long-term exposure to steady-state noise. The end result in either case may be hearing loss, but with impulse noise a single unprotected exposure can produce a permanent effect. . These effects depend on individual susceptibility, which is something we cannot yet predict. So we try to prevent any harmful exposure and we warn that the damage could easily be permanent and irreversible. The risk has long been thought to be correlated to the peak level of the noise and to the B-duration of the impulse, a measure of the time it takes for the impulse noise to decay to levels 20 dB lower than the peak level. These characterizations of the impulse sound were used in MIL-STD 1474 for many years to determine how many rounds per day could be safely fired, assuming single or double hearing protection were used.

The characterization of "safe" exposure within the MIL-STD limits does not mean there is no possibility of damage occurring. The Military considers the exposure to be safe as long as no more than 5% of the exposed population will be materially impaired. The allowable number of rounds (ANOR) for typical small arms weapons have been very high, permitting many thousands of rounds to be fired per day, but it is emphasized that this number is generated assuming appropriate hearing protection is worn. Without hearing protection a single round has some risk of causing a permanent threshold shift.

This dependency on peak level and B-duration has given way in version E of MIL STD 1474 to more updated criteria that look at the overall energy or waveform shape produced by the weapon. A dBA value is assigned to the

sound (using one criterion) or the Acoustical Risk Units associated with the sound is assigned (using the other). The medical community in the Army, which used to use MIL-STD 1474 as the medical criterion, is waiting for additional research to prove out the new design criteria. Meantime, the medical community uses a modification of the peak level/B-duration characterization for risk assessment purposes. This is designated as the interim impulse noise medical criterion. For small arms fire there is no difference in the medically determined ANOR between what was calculated under the old standard and the interim standard. The ANOR for small arms fire is reduced considerably, however, when the newer design criteria are used, from thousands of rounds to perhaps hundreds.

These days, indoor firing ranges are becoming more common. The noise associated with indoor ranges sounds very different than for outdoor ranges, due to reflections. Peak levels at gunner or adjacent shooter positions do not change from those identified for outdoor ranges (the shock wave arrives as the shooter location continues to expand and thus has lower pressure levels associated with it by the time it gets reflected). But the reflections affect the B-duration, depending on how much acoustical treatment is applied to reflective surfaces. Large indoor ranges, with many shooters firing simultaneously, make the range noise quasi-steady-state. When that happens, the risk associated with incurring hearing loss better ties to the dBA level of the din, like the newer criteria promote.

Machine gun firing deserves special mention here. Each shot fired by a machine gun carries with it the hearing hazard that would be commensurate with the acoustical characteristics of that shot, just as it would be for a rifle or hand gun. But when fired in bursts the hazard takes on attributes more typically associated with steady-state noise. In fact, when the bursts last for one or more seconds in duration, we evaluate the dBA level of that burst separately and in addition to the peak level, to determine risk. Often, the dBA level examination suggest the steady-state aspect of the noise is worse than the impulse aspect.

And this is particularly true for machine guns mounted on helicopter platforms. That is because the machine gun muzzle is often closer to the helicopter crew's ears, both in an axial and lateral direction. Consequently the level is high. Sometimes the helicopter fuselage provides some protection, but not always. Many platforms are flown with doors removed and therefore the sound travels directly from the machine gun to the crew's ears. All these considerations taken together may mean that there are severe restrictions associated with safe machine gun fire, even when double hearing protection is used.

Large Caliber Weapon Systems

Soldiers may also use more powerful weapon systems than small arms. We lump the systems into a category we call large caliber weapon systems, and these include mortars, howitzers, and shoulder-fired arms. These weapon systems come in a variety of shapes and sizes, and fire bullets of many different kinds. The one thing they all have in common is that because they fire larger bullets, greater amounts of propellant are used and hence they make more noise. They also place the crew using these systems in different spatial relationships with the noise that comes out of the weapon. The mortar gunner, for example, after dropping the round into the mortar tube, is very close to the weapon muzzle. The gunners firing a shoulder fired weapon get exposed to two blast waves: the one coming from the front of the tube, the other from the back end of the tube. These systems are also often fired from protected areas, including from inside an enclosed space, and thus they also get bombarded by sound reflections.

Both shoulder fired weapons and howitzers fire cartridges with specific propellant weights selected according to where the firing team wants to place the warhead. The weapon noise will depend on the charge weight. At the top charge, the pressures associated with the muzzle blast may be high enough to cause more bodily harm than just hearing loss. The concussive sounds may be capable of causing eardrum rupture or bruising of internal organs, particularly the lungs. Additional firing restrictions beyond just limiting the number of rounds that may be fired in a given day and the kind of hearing protection determined from hearing damage criteria may be required.

Howitzers and mortars may also be subject to secondary detonation, sometimes called flashing. This is when the material expelled from the barrel include some unburnt propellant. When this material leaves the gun, it is resupplied with fresh oxygen, and because it is hot, it may generate a new fireball and blast wave, which because it is unrestrained by the weapon, can be even louder than the original muzzle blast at crew positions.

Other Impulse Sounds Associated with Explosions

Army personnel may also be exposed to loud impulse sounds due to exploding ordnance. In some cases, particular those associated with use of explosives as shaped charges to gain entry to closed-off areas, the exposure is intentional. Breachers, for example, may be near the explosion, with minimal protection from the blast wave. Levels can certainly be at or near those associated with large caliber weapon systems. With exploding ordinance, there

are also the sounds associated with the shock waves generated by the outwardly moving explosion fragments. They act as precursors to the main blast, and may, according to the newer design criteria, be more harmful to hearing than the actual blast wave. There have been some interesting materials published, for example, on this aspect for the ordnance known as the Bangalore Torpedo, which is a device used for clearing pathways through barbed wire.

Then there is the whole topic of Improvised Explosive Devices, or IEDs. These are booby traps planted by enemy forces to kill and maim our fighting forces. Soldiers exposed to IEDs may be on foot patrol, or inside vehicles, but these devices are certainly threats to life and limb in both cases, depending on their construction. There is essentially no limit to how loud an IED can be. But the point is that if you were to be in the middle of an explosion, your hearing may be the least of your worries. Nonetheless, it must be mentioned that this is a source for high noise exposure in the life of a Soldier.

Steady-State Noise

Almost all vehicles in the Army will expose crew and passengers to hazardous levels of noise during some operating condition. Wheeled transports will expose occupants to 85 dBA or more levels when travelling at high speeds with climate controls systems on and/or with windows or hatches open. Spartan interiors and noise sources are mostly designed with function in mind; noise control is low on the totem-pole of priorities. Some specialty equipment, including mine-detectors may operate at safe noise levels because the crew member operating the vehicle is located high up, far from the vehicle noise sources. Generally speaking, wheeled vehicles top out with noise in the mid-90 dBA range. Single hearing protection is generally required when in or operating these vehicles.

Occupants of tracked vehicles are exposed to higher sound levels than wheeled ones when the vehicle is in motion, and the levels rise with increased travel speed. There is some variability in levels associated with occupant location and hatch condition, but levels exceeding 110 dBA are often reached. Double hearing protection is generally required when in these platforms, and in some cases, there may be restrictions in permitted travel distances (which are considered equivalent to operating time at specific speeds).

Vehicular noise may be compounded by noise from weapon systems such as mortars, missiles, grenade launchers, or machine guns that may be integrated into the vehicle platform.

Aircraft

The Army rotary wing aircraft platforms are also inherently noisy. All interior environments are in the high-90 to low-100 dBA range at minimum, and can reach close to 110 dBA in the noisier platforms. Double hearing protection is the norm.

Aircraft that are designed as offensive weapon systems have additional noise issues. Some may be flown with crew unprotected by shielding provided by the fuselage. Worse still, open door flying on some platforms not only places the platform mounted weapon systems (machine guns, missiles, or rockets) with the noise sources close to the crew, but at a more downrange location relative to the line of fire. Recalling that muzzle blast is usually greater the closer the receiver is with respect to radial angle relative to the line of fire. Typically, even with double hearing protection, significant restrictions may be placed on the daily number of rounds that can be safely fired.

Fixed wing aircraft have similar cabin noise levels. Noise sources range from 105 to 122 dBA. Sources include engine and propeller noise and flow noise. In tactical aircraft, avionics cooling air is a primary noise source due to high air velocities.

Flight lines

Flight lines are typically well above double hearing requirements. The Services have different aircraft operating protocols. For fixed base operations, minimal personal are adjacent to aircraft upon engine start. Aircraft then taxi clear of personal to the runway. For aircraft carriers, those operations occur in the confines of 4 and a half acres. Furthermore, there will be a mix of aircraft operations, including launch and recovery, re-fueling and occasional maintenance with flight deck personal. Numerous aircraft are operating in very close proximity requiring the directions from aircraft directors (yellow shirts). Add to the mix, safety, fueling, maintenance and fire personnel. There can be on the order of 150 – 200 personnel on the flight deck. The "quiet" spots are on the order of 126 dBA. For a carrier launch, aircraft are hooked to the catapult and restrained while the aircraft goes to full power for final aircraft checks. These noise levels for tactical jets are on the order of 148 dBA and lower for propeller aircraft.

Numerous acoustic measurements have been made directly below the catapults which are typically berthing spaces or ready rooms. Through modelling and verification measurements, the acoustic energy propagates

through ship's structure and re-radiates into the manned spaces. The noise levels in these spaces range from 87 to 102 dBA. Activities in these areas include squadron briefings to mundane activities such as sleeping. Aircraft recovery (landings) are similar in that the aircraft land at full power as they capture the arresting gear wire. That wire initially pays out at aircraft speed and slaps the flight deck as the aircraft is stopped. This generates numerous acoustic transients as well as the noise of the aircraft at full power.

In the off-hours, personnel will have meals on the mess deck which can have noise levels of 92 – 94 dBA. Or they can do their laundry which is in the lower aft end to the ship. These noise levels have been measured at 105 dBA. Machinery spaces and engine rooms also add to the din of noise exposures. Including other classes of ships (besides aircraft carriers) engine room have been measured from 85 to 118 dBA. For reference, diesel powered engine rooms tend to be 108 to 118 dBA with lots of low frequency energy from the engine and high frequency if the diesel engine is turbo-charged. Other shipboard noise sources are hydraulic systems (elevators), vent fans, pumping systems and ventilation systems.

Garrison Activities

There are many occupations within the Army that are similar to their industrial counterparts and the work environments in both are going to be similar. For example, motor pools use the same kind of noisy equipment their counterparts in industry use. The same is true for machine shops, food preparation areas and the like. Some differences in productions levels may exist in smaller operations compared to their industrial counterparts, because their existence is not necessarily the same. But generally speaking you will find virtually every kind of industrial operation somewhere in the Army. Of note, there are some operations that are notoriously noisy, such as sandblasting at rework facilities, where levels can reach into the 120-plus dBA range.

Some Words about Hearing Protection

Much reliance is placed on using hearing protection to mitigate the adverse aspects of noise exposure. And these devices are certainly capable of protecting Soldiers. In fact, audiologists have been known to say that there is no hearing loss found among Soldiers who properly use well-fitted hearing protection. But the caveats are not always met. Soldiers are often under-trained with regard to how their hearing protectors should be worn, so they wind up not providing the ear canal seal they need to be effective sound blockers. Often the ear plug devices are not inserted deeply enough, so they may "leak,"

presenting a path for noise to get inside the ear. Often Soldiers are simply issued hearing protection, without proper attention to how well they fit or the attenuation needed for their work assignment. Many ear plug devices come in different sizes, and there is a reason for that. Our ears come in different sizes. Even an individual can have different sizes for each of their two ears. Also, hearing protectors can wear out, becoming mal-formed or dried out. They require maintenance to be completely effective.

Proper use and proper fitting are thus key elements in effective hearing protection. But far and away the most important aspect is whether the hearing protector is worn and worn consistently. Historically, Soldiers were reluctant to wear hearing protection, and for good reason. Dismounted Soldiers on patrol need to hear relatively quiet sounds to be aware of what's going on in their surroundings. Their lives depend on that situational awareness. But anything put into the ears affects that ability, and makes it more difficult to localize where a sound is coming from. For these reasons, the Army has made a new kind of hearing protector available…the level-dependent or non-linear earplug.

Level-dependent protectors do not effectively block quiet sounds, but do shut out transmission of high-level noise associated with gunfire. Some devices do this passively, though the action of a small tube embedded in the device that filters out the loud sounds. Other devices, which are more sophisticated (and therefore more expensive) do this electronically. All these devices allow for improved situational awareness over the ordinary hearing protector. They are not perfect, and require a period of training to approach the performance one would get from the naked ear, but their performance is improving. The existence of these new devices has already generated a sea-change in the Army culture with regard to expecting hearing loss as a part of being a Soldier. Hearing loss is preventable.

One aspect of hearing protector use that not all Soldiers are aware of is the adverse effect of not being consistent when wearing the devices. Here's an example. If a Soldier were to be transported in a vehicle with a 106 dBA level, and that Soldier were to put his hearing protection in after the vehicle was in motion, he would receive about 33% of his allowable daily noise exposure per minute of being unprotected. That Soldier should be wearing the hearing protection prior to entering the transport, and not waiting for the vehicle to start moving. Similar things could be said about unprotected exposure to impulse noise. However, the situation with impulse noise is compounded in that the hearing damage caused by exposure to impulse noise is believed to be mechanical in nature. Mechanisms in the ear can permanently break. Therefore

unprotected exposure to even one or two rounds can cause permanent damage.

To facilitate the practice of preventing hearing loss, the Army has a long-established Hearing Program. Changes to the Army Hearing Program (AHP) occur based upon noise exposures, environmental factors, hearing health education needs and hearing test data reviews and reports, for Soldiers and Civilians alike. All Army personnel, and Soldiers in particular, who are exposed to hazardous noise have seen considerable improvement in hearing ability since 1974 with hearing health being maintained and even improved during recent combat operations. Rates of significant hearing loss (>H-1 hearing profile) in Combat Arms Soldiers have decreased from 34-40% in 1974, to 14-20% in 1989, and 7-10% from 2000-2014. Even so, no amount of occupational hearing loss should be acceptable; hearing loss rates can be lowered still. Consistent and active Command, Soldier, and Civilian acknowledgement about, and support for, the importance of hearing for training, for combat, and for communication throughout life, will continue to decrease preventable hearing loss rates.

Occupational Noise Exposure and Hearing Loss

Themann, Christa L, MA, CCC-A and Masterson, Elizabeth A., PhD, CPH, COHC

Exposure to hazardous noise is one of the most common occupational risks, both in the U.S. and worldwide. An estimated 22 million workers are exposed to high levels of noise on the job each year in the U.S. and 25% of U.S. workers have a history of occupational noise exposure at some point in their careers. Nearly one-fourth of hearing losses in the U.S. working population can be attributed to occupational exposures. Worldwide, occupational noise exposure accounts for 16% of adult-onset hearing loss and 18% of Disability-Adjusted Life Years (DALYs). Occupational noise exposure remains a highly-prevalent workplace hazard, despite decades of regulation and preventive efforts.

Permanent sensorineural hearing loss is the most common and most serious effect of exposure to high noise levels. Noise-induced hearing loss (NIHL) is characterized by a "notch" in audiometric thresholds occurring in the 3000-6000 Hz range with threshold improvement at higher frequencies. Most occupational noise-induced hearing losses are bilateral, although unilateral notches can occur when noise exposure is substantially louder in one ear than the other. Hearing loss from noise accumulates most quickly in the early years of

exposure and slows over time as exposure continues. Noise-induced hearing loss is caused by damage to the outer cochlear hair cells; however, recent evidence indicates that noise exposure can also damage the synapse between the hair cells and auditory neurons. This "synaptopathy" results in a "hidden" hearing loss which is not evident on the audiogram but manifests itself in more challenging hearing tasks such as understanding speech in noise. Other effects of occupational noise exposure include tinnitus and communication interference. Certain non-auditory effects have been associated with noise exposure, including hypertension, changes in blood chemistry, and stress. Occupational noise exposure has also been associated with poorer job performance, accident risk, and absenteeism.

Risk of occupational hearing loss varies by age (higher prevalence with increasing age), sex (higher prevalence among males), and race (higher prevalence among whites). Risk varies across countries, with the highest prevalences in China and Papua New Guinea and the lowest in Australia and New Zealand. Within the U.S., risk also varies somewhat across geographical region, but may reflect the predominant industries in each region.

Prevalence of noise exposure and risk of occupational hearing loss vary across industries and occupations. In the U.S., workers in the Mining, Construction, and certain Manufacturing industries have the highest risk of hearing loss. However, workers in certain industries typically considered to have low levels of noise exposure – such as the Real Estate and Rental and Leasing industry and the Healthcare and Social Assistance sector (as defined by the North American Industry Classification System [NAICS]) – have also been shown to have a high prevalence of hearing loss. In the thirty-year period between 1981 and 2010, the prevalence of hearing loss among noise-exposed workers across all industries combined decreased less than 1% in the U.S. The prevalence remained essentially stable within most individual industries; however, the prevalence increased substantially in the Healthcare and Social Assistance sector while declining in the Agriculture, Forestry, Fishing and Hunting sector. Although hearing loss prevalence has remained largely constant among noise-exposed workers, incident (new) cases of hearing loss have slowly declined in most U.S. industries and the overall adjusted risk of incident hearing loss among noise-exposed workers has decreased 46% over twenty-five years (1986-2010).

Persons with auditory damage caused by noise frequently do not recognize it. One in four U.S. adults who reported excellent or good hearing had audiometric evidence of noise damage. Most noise-exposed individuals fail to

take basic precautions to prevent hearing loss, such as wear hearing protection. Thirty-four percent of noise-exposed workers report not wearing hearing protection.

Noise exposure and occupational hearing loss remain highly prevalent in the U.S. and worldwide. Occupational noise exposure is regulated in most developed countries, including the U.S. However, lack of emphasis on noise control, over-reliance on hearing protection, lack of worker training, and a general overall failure to recognize the impact of hearing loss on quality of life likely contribute to the continuing high burden of hearing loss among noise-exposed workers. An integrated public health approach is needed to make strides in prevention.

This review will examine the critical public health problems of occupational noise exposure and hearing loss. The paper will briefly describe mechanisms of damage, configuration and progression of hearing loss, other auditory (e.g., tinnitus) and non-auditory (e.g., cardiovascular) effects of exposure, and economic burden. Differences in prevalence, incidence, and risk of hearing loss across industries, occupations, and demographic variables will be discussed. The contributing factors for this continued public health issue, such as cultural acceptance of loud noise, de-emphasis on noise control in the workplace, and a lack of hearing protection use when engineering controls are not present, will also be explored. Finally, recommendations, including an integrated public health approach and the potential benefit of pharmaceuticals, will be presented.

Human Exposures and their associated hearing loss profiles: Professional Musicians, Soundboard Engineers, and DJs

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Exposure to sounds of sufficient intensity and duration has been shown to cause several auditory effects in humans, known categorically as Noise-Induced Hearing Disorders (NIHD). Noise-Induced Hearing loss (NIHL) is the most commonly discussed and researched condition due in part to the high prevalence in large populations such as military personnel and industrial workers. Tinnitus, hyperacusis, diplacusis, and dysacusis are other auditory disorders which result from excessive sound exposure.

Music industry professionals can be considered a uniquely vulnerable population to NIHDs. This is due to several factors including high probability for routine exposure to sound levels known to be detrimental to hearing, the integral relationship between auditory health and primary occupational performance, and participation in an unregulated industry. High variability of occupational settings, schedules, and sound sources further complicates characterization of individuals in the many subpopulations of music industry professionals. Key subpopulations with unique considerations include performing musicians, audio engineers, recording personnel, music educators and students, and performance support staff. In live music settings, the audience can be considered a secondary or contingent population since their exposure is directly affected by the behavior of the performers, technical and support professionals.

When the primary damaging sound source is music, the resultant conditions are termed Music Induced Hearing Disorders (MIHD). Though there exists some controversy regarding the relative damage-risk criteria of steady-state industrial noise and music signals (Szibor et al., 2017; Strasser, et al., 2008), the marked increase in prevalence of MIHDs in music industry professionals as compared to the general population (Schink et al., 2014) indicates that music should be considered a potentially damaging stimuli.

The hearing loss profile of musicians is often considered comparable to that of other noise-exposed populations. This is partially due to the similarities between the macro acoustic qualities of music and what is generally considered to be noise, and partially due to the compound nature of sound exposure: music is often not the only sound a musician will be exposed to in their daily lives. MIHL is characterized by a gradual loss of auditory threshold sensitivity in a high-mid frequency region of hearing, with the classic presentation being identified as a sensorineural hearing loss 'notch' centered in the 3k - 6k Hz region. Since an individual's two ears share approximately the same physical and temporal coordinates in a given soundscape, NIHL are generally bilateral and symmetric in degree. However, musicians demonstrate a high prevalence of asymmetric hearing loss attributable the physical laterality characteristics of their primary instrument and location within an ensemble (Chasin, 2006; Jesper Hvass Schmidt et al., 2011). For instance, the violin disproportionately exposes the player's left ear to the instrument's sound while the flute similarly affects the player's right ear. Reduced auditory thresholds in the extended high frequency audiometric (EHFA) range (>8k Hz) has been suggested to be a more sensitive indicator to auditory damage as compared to conventional audiometric range (125 – 8k Hz) (Kazkayasi et al, 2006; Dunckley et al, in publication).

The vocational impacts of MIHD are far-reaching and vary primarily as a factor of one's work setting and role. For example, a new development of mild NIHL may go unnoticed by a touring rock musician, but may be career-limiting to a record mastering engineer or audio archivist. Generally, the MIHD which cause the highest pressure for career path changes are not hearing loss but instead tinnitus, hyperacusis, diplacusis, and dysacusis. Chronic bothersome tinnitus may dramatically reduce one's trust in their auditory perceptual abilities when critical listening is required for their work, and can inhibit both focus and enjoyment for performance-based roles. Hyperacusis severely limits one's capacity to tolerate the inherent loudness in the majority of professional music settings, thereby limiting participation in rehearsals, performances, studio sessions, and support work in venues. Diplacusis and dysacusis erode one's sense of pitch stability, which is an inhibition for the proper execution of tasks requiring critical listening (editing, mixing, and mastering) and is a major handicap for the performance of continuous pitch instruments (bowed strings, voice, tympani, etc).

Traditional interventions designed to mediate acquired hearing damage necessitate the reduction of an individual's exposed intensity, duration of exposure, or both. Technological methods to reduce exposure intensity include personal-wear products (custom filtered uniform-attenuation earplugs and custom molded in-ear monitors) as well as externally deployed products (acoustic barriers, sound absorptive devices, and specially designed spaces for the control and routing of sound signals such as recording studios). Though technology has improved significantly in the last several decades to afford higher-fidelity listening and greater acoustic control with these devices, none are without compromise of the original acoustic signal and even the best demand the user to adjust and 'ear-train' to their proper use. Methods to reduce an individual's duration of exposure are numerous including, but not limited to, reduction of personal practice time, deconstruction of ensemble rehearsals into smaller sectional groups, and strategic programming of performances.

The availability of a pharmaceutical intervention with proven efficacy at reducing the adverse effects of sound exposure on the auditory system would constitute a notable change in available MIHD intervention options for musicians. Reduction of risk equates a reduction in individual reliance on traditional personal-wear and externally deployed interventions, and thus many benefits that accompany that change, not the least of which being decreased barriers to end-user acceptance and intervention program buy-in.

Adult Exposure to Loud Music: Recommended Exposure Limit for Non-Occupational Music in Adults

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Noise is among the most common occupational and recreational exposures globally, and the burden of noise-induced hearing loss (NIHL) is quite high as a result. The WHO estimates that approximately 466 million people worldwide have a disabling hearing loss, and other sources estimate that roughly 16% of all hearing loss cases are NIHL, suggesting that nearly 75 million people suffer from NIHL globally. Occupational exposure limits for noise have been in place in many countries for decades, and occupational NIHL has declined in some countries as a result. An appropriate limit for non-occupational noise exposures has not been debated scientifically for more than 20 years, and, in the meantime, a number of sources have suggested that occupational exposure limits ought to serve as de facto recommended non-occupational (e.g., music exposure) limits. The purpose of this summary is to assess whether existing exposure limits used for occupational noise exposure are suitable for determination of risk due to non-occupational music exposures, specifically exposures to recorded music.

Occupational and nonoccupational exposure limits represent political compromises and are typically not solely evidence-based. The vast majority of nations and regulatory agencies around the globe have specified an 8-hour time-weighted exposure limit for occupational noise of 85 dBA using a 3 dB time-intensity exchange rate. To completely eliminate the risk of any measurable noise-induced hearing loss in any exposed individual across audiometric frequencies of 0.5-6 kHz, the appropriate exposure limit would be a 24-equivalent continuous exposure level (L_{EQ}) limit of 70 dBA with a time-intensity exchange rate of 3 dB, which is equivalent to an 8-hour exposure L_{EX} of 75 dBA (assuming that the average noise level for the remaining 16 hours of the day is 60 dBA or less). A 24-hour L_{EQ} limit of 75 dBA (energetically equivalent to an 8-hour L_{EX} of 80 dBA) is expected to result in an excess risk of a material hearing impairment of less than 1% (i.e., < 1 out of 100 workers exposed at this level would have a material hearing impairment after 40 years of daily exposure). By contrast, the exposure limit used by the US Occupational Safety and Health Administration (OSHA), which specifies a 90 dBA TWA and 5 dB time-intensity

exchange rate, will result in an excess risk of a material impairment of approximately 25% (i.e., 1 out of 4 workers exposed at this level would have a material impairment after 40 years of daily exposure).

Non-occupational music exposures differ in important ways from occupational exposures, chiefly in that they are often considered desirable. The temporary effects of occupational noise exposures (i.e., the induction of a temporary threshold shift, or TTS) may be worse than those of some types of energetically-equivalent music. However, the tremendous variation in types of music warrant the adoption of conservative exposure guidelines that presume exposure to the most harmful types of sound, and this report therefore recommends that exposure limits developed for noise be considered applicable to music exposures. Furthermore, there is evidence that music listening patterns differ substantially from patterns of occupational noise exposure, and exposure durations are potentially substantially higher for music exposure. The broadly-accepted, energy-based assumptions regarding risk of hearing loss from noise exposures in national and international standards presume that varying temporal patterns of exposure do not influence risk of hearing loss. These standards assume a daily exposure duration of no more than 12 hours, which occurs infrequently with regards to occupational noise as well as to music exposures. Therefore, application of the existing NIHL models to prediction of hearing loss from music is considered appropriate, with the important caveat that these models are not intended to predict loss over durations greater than 40 years. It is also assumed, based on the literature documenting maximum output levels of portable audio systems, that non-occupational music exposures do not exceed levels necessary to cause acoustic trauma (immediate, permanent damage to the auditory system).

Without a specified definition of maximum acceptable noise-induced permanent threshold shift, it is not possible to determine the risk of individuals meeting or exceeding that definition following exposure to music, and in turn impossible to determine an acceptable level of risk of NIHL. Nevertheless, this review has concluded that the adoption of the most protective occupational noise exposure limit, European Union Directive 2003/10/EC, i.e., the lower exposure action value of 80 dBA 8-hour L_{EX}, which is energetically equivalent to recommendations from the US EPA and WHO for nonoccupational noise of 75 dBA L_{EQ} over a 24-hour period, is warranted for the purposes of minimizing risk for music-induced hearing loss in children and adults. Adoption of an 80 dBA 8-hour L_{EX} (i.e., 75 dBA 24-hour L_{EQ}; 89 dBA 1-hour L_{EQ}) limit for exposure to music

likely represents an optimal trade-off between being sufficiently protective and being onerous and/or technically, commercially, or socially infeasible.

Alternative exposure limits might be considered appropriate, if the user of these guidelines wishes to establish greater restriction on exposure limits (and eliminate any risk for music-induced hearing loss) or lesser restriction on exposure limits (accepting higher risk for music-induced hearing loss). To eliminate risk for music-induced hearing loss, an appropriate exposure limit is 75 dBA 8-hour L_{EX} (i.e., 70 dBA 24-hour L_{EQ}; 84 dBA 1-hour L_{EQ}). This limit might be appropriate for young children or those without have the autonomy to make informed personal health decisions, persons with pre-existing NIHL, or persons with increased susceptibility to NIHL. A less restrictive exposure limit, applicable to individuals willing to tolerate modest risk for a small degree of NIPTS, but still sufficiently protective of the vast majority of people exposed to non-occupational music exposures, is 83 dBA 8-hour L_{EX} (i.e., 78 dBA 24-hour L_{EQ}; 92 dBA 1-hour L_{EQ}). Regardless of which limit is adopted, effective educational measures will be required to inform the exposed public of these recommended limits.

Childhood Exposure to Loud Sound: Available Evidence and Recommended Noise Exposure Limit for Children and Young Adults in Recreational Settings

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Noise is one of the most common environmental exposures and is experienced by almost everyone on a daily basis. It is universally recognized that prolonged exposure to high levels of non-impulsive noise (hereafter referred to as "noise") will lead to noise-induced hearing loss (NIHL). These high levels of noise have traditionally been found in an occupational setting, but exposure to high levels of noise is increasingly common in recreational settings.

Special consideration must be given to the effects of noise exposure on children and young adults as hearing loss can result in lower scholastic achievement, social isolation from their peers, and reduced earning potential. Children (those under 18 years old) are also more likely than adults to regularly engage in behavior that increases their exposure to high levels of noise such as attending concerts and sports events, or using a personal music player. A study

published by Rabinowitz et al. in 2006 found that approximately 16% of young adults entering the US workforce had hearing loss exceeding 15 dB at the 3, 4, or 6 kHz audiometric test frequencies (Rabinowitz et al. 2006). Since that time the use of personal listening devices has increased and it has been suggested that the percentage of young adults with detectable levels of hearing loss will consequently increase. This presents an issue for the U.S. armed forces as hearing loss is already one of the most common medical disqualifications for first time recruits (Walter Reed Army Institute of Research 2018). Even recruits who are admitted with less than disqualifying hearing loss (i.e. < 30 dB HL averaged at 0.5, 1.0, and 2.0 kHz, < 45 dB HL at 3.0 kHz, or <55 dB HL at 4.0 kHz) may be expected to have reduced fitness for duty (Military.com).

While occupational exposure limits for noise have been established and it is possible to extrapolate these exposure limits from a standard eight hours/day, five days/week work schedule to non-standard work schedules, these occupational exposure limits were developed based on economic, technical, and political feasibility and are not purely health-based. Regulatory occupational exposure limits inherently allow for a certain "acceptable" level of NIHL after a standard working lifetime and were not designed to consider vulnerable populations such as children. In addition, the duration and frequency of recreational noise exposure may differ greatly from that of occupational noise, making it inappropriate to simply adopt occupational exposure limits as a limit for recreational noise. The United States Environmental Protection Agency (EPA) and the World Health Organization (WHO) have suggested exposure limits for the general environment and certain recreational activities, but these exposure limits are not specific to children or young adults and do not always specify the estimated risk of NIHL at the recommended exposure levels. While these recommended exposure limits are more protective than occupational limits, and thus more suitable for use in vulnerable population groups, there is limited evidence to support their application to children.

There is currently no established acceptable risk of hearing loss in children. Therefore, this report assumed that the most appropriate exposure limit for recreational noise exposure in children would be developed to protect 99% of children from hearing loss exceeding 5 dB at the 4 kHz audiometric test frequency after 18 years of noise exposure, e.g., be essentially completely protective against NIHL. Using the International Organization for Standardization (ISO) 1999:2013 model for predicting hearing loss, it was estimated that noise exposure equivalent to an 8-hour L_{EX} (i.e. 3 dB exchange rate) of 82 dBA would result in about 4.2 dB or less of hearing loss in 99 percent of children after 18

years of exposure. To further ensure that the risk of hearing loss in children is reduce, the 8-hour L_{EX} was reduced to 80 dB by including a 2 dB margin of safety. This 8-hr L_{EX} of 80 dBA is estimated to result in 2.1 dB or less of hearing loss in 99 percent of children after 18 years of exposure. This is equivalent to 75 dBA as a 24-hour L_{EQ}. Previous reviews of the literature have indicated that recreational noise exposure often exceeds these levels and that children and young adults may be at the risk of developing NIHL prior to their entry to workforce or armed forces.

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Section 2: Factors that Influence Individual Variability in Vulnerability to Noise Injury: What are the Factors that might Influence Risks and Benefits for Individual Patients? What is the Potential Impact of Such Factors on Clinical Trial Design?

The effects of external- and middle-ear filtering on noise-induced hearing loss revisited: New data and the possible protective effects of middle-ear nonlinearity and perforation of the eardrum

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In an earlier report (Rosowski, 1991) we used a data-based model analysis of sound power flow through the auditory periphery to demonstrate the combined action of the external and middle-ear in gathering and filtering the sound intensity of impulsive noises that reached the inner ear. The largest effects of this filtering were: (1) a frequency dependent 10 to 40 dB reduction in intensity at frequencies less than 800 Hz, with the largest losses at the lowest frequencies, and (2) similar-sized losses at frequencies above 4 kHz. The smallest losses in conducted intensity occurred in the 1 to 4 kHz frequency range in the region of the most sensitive hearing thresholds.

For humans, this model analysis depended on multiple measurements made over the previous 25 years, including: measurements of external-ear function by Shaw and colleagues (1974), measurements of middle-ear input admittance by Rabinowitz (1982), measurements of stapes velocity in cadaveric ears by Kringlebotn and Gundersen (1985), and model predictions of the inner-ear input impedance by Zwislocki (1965). The analyses computed the sound power that was gathered by the external and middle ear from the environment, and the fraction of that power that was passed onto the inner ear. The basic conclusions were: (1) The low-frequency impedance mismatch between the stiffness controlled middle ear and the mass-inertance associated with free-field sound flow greatly reduced the absorption of sound intensity at frequencies below 1000 Hz. (2) The human middle ear was an inefficient conductor of sound power, especially at frequencies above 3 to 4 kHz. (3) Projections of the free-

field sound intensity required to produce a power level in the human ear of 10^{-18} Watts well approximated the human threshold curve.

We propose to update this analysis by using an extensive set of more recent data, including: the acoustic reflectance measurements of Keefe et al. (1993); Voss and Allen (1994) and others; and the middle-ear transmission and cochlear-input impedance data of Aibara et al. (2001); Puria et al. (2003); Nakajima et al. (2009) in human cadavers, and Chien et al. (2009) in live ears. We will also use circuit models (e.g. O'Connor and Puria 2008) to evaluate our updated findings and investigate the effects of middle-ear nonlinearities and eardrum perforations on the gathering of high sound intensities and their transmission through the middle ear. The addition of nonlinear elements will be driven by preliminary data gathered by us on sound-induced motions of the eardrum and the stapes to high-level sound stimuli (Cheng at al. 2017). Perforations will be modeled using the analysis of Voss et al. (2001), and model outputs compared to preliminary measurements of the effect of eardrum perforations on the stapes motions produce by high-level sound (Cheng et al. 2018).

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On the need to control acoustical and mechanical differences in studies of pharmaceutical interventions for hearing loss

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The cochlea is the target organ for Pharmaceutical Interventions for Hearing Loss (PIHL), but the cochlea is not accessible directly by many interventions or by the agent (e.g., noise) producing the damage. The study of efficacy (i.e., effect under ideal conditions) and effectiveness (i.e., effect under practical conditions) of candidate pharmaceutical agents requires careful study design, including consideration of the intersubject differences in the auditory transduction pathway through the outer and middle ear, including monitoring for any effects of middle ear muscle contractions (MEMC).

Between-subject designs are preferred in pharmaceutical studies, especially for Phase III trials. Between-subject designs include larger numbers of participants with each participant receiving only one intervention, which increases the external validity of the study at the cost of increased study size. Within-subjects designs, in which all participants receive all interventions, also have the often-overlooked limitation that the results generalize only to a population of participants who have been exposed to all interventions (Kirk, 1995).

Increased within-group variance reduces statistical power. If the variance within the group assigned to one treatment arm is random, statistical power can be restored by increasing the size of the study using long-established procedures (e.g., Cohen, 1988). Systematic within-group variance is not managed so easily, however. Systematic within-group variance challenges a fundamental assumption of many inferential statistical methods, which is that the variance not associated with the intervention is normally and independently distributed. Furthermore, systematic variance reduces effect size (Flamme, 2001) and therefore statistical power, which could lead investigators to discard beneficial pharmaceutical interventions.

Randomization is a powerful way of reducing selection bias and minimizing between-group differences on nuisance variables, but randomization only produces an asymptotic expectation of equivalent groups at pretest (Shadish et al., 2002). Significant group-level pretest differences can remain after random assignment, particularly when groups are small, heterogeneous, or when many factors influence the intervention. In small studies it is crucial to ensure that the study design and analytic methods control for key sources of variance to the greatest extent possible.

It is also possible to minimize the consequences of systematic within-group variance using larger sample sizes or special statistical methods that are robust to violations of this assumption (e.g., Huber, 1967), but it is prudent to manage

systematic variance through study design or by controlling the source of variance in the analytic models used.

For example, the outer and middle ears are sources of intersubject differences, and therefore within-group variance. Substantial intersubject differences exist in the head-related transfer function (HRTF) (i.e., the acoustic effect of the listener's torso, head, and external ear on the signal reaching the middle ear) and the middle ear transfer function (i.e., the transfer of mechanical energy between the tympanic membrane and the medial surface of the oval window). These intersubject differences in HRTFs and middle ear transfer functions are measurable using commercially-available instrumentation and therefore can be used to manage within-group variance either as a blocking factor in the study design or as a covariate during data analyses.

MEMCs, an additional source of intersubject differences, could alter the impedance of the middle ear system and, if activated, could modify the amount of exposure received by the participant in a PIHL study. The amount of impedance change might correspond to as much as a 20-dB reduction in exposure for low-frequency signals if the middle ear muscles are fully contracted during presentations of acoustic stimuli.

Our submission to this special issue describes a study evaluating the likelihood of and factors correlated with MEMC among listeners with excellent hearing sensitivity. Elicitor stimuli included tones, white noise, and recorded gunshots. White noise and 1 kHz tonal elicitors were the most likely to elicit reflexive MEMCs, and although no stimulus produced the MEMC proportions necessary for inclusion in damage-risk criteria (i.e., 95 % confidence of 95 % prevalence), all stimuli evaluated in the study elicited MEMC in at least 10 % of the participants. MEMC could, therefore, be an effect modifier in a PIHL study, especially if that study includes controlled exposures to signals with significant low-frequency energy. These contractions, along with individual differences in outer and middle ear transfer functions, should be controlled in PIHL studies to ensure that resources devoted to the development of these pharmaceutical agents have maximal utility.

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Genetic Analysis of Noise-Induced Hearing Loss and Tinnitus: A Pathway to Discovery

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Tinnitus and hearing loss have been the VA's #1 and #2 service-connected disabilities since 2006, now costing over two billion dollars per year in compensation and in 2015 over 2.6 million Veterans received disability payments for these types of auditory damage. A study of 570,248 Iraq and Afghanistan Veterans seen at the VA found 7.3% with a diagnosis of hearing loss, 6% with tinnitus, and another 5.6% with both. Servicemembers 26 years of age and under constituted 36.48% of this cohort (Swan, 2017). Traumatic brain injury (TBI), the signature injury in recent wars, more than doubles the risk of tinnitus during deployment (Yurgil, 2016). Nevertheless, genes that underlie susceptibility to tinnitus have not been identified and there is no cure or definitive treatment.

Loss of hearing is a serious handicap, primarily due to its effect on communication. Given the critical role of verbal communication in an economy increasingly dominated by interpersonal skills, loss of hearing has a strong impact on employability. Hearing loss can lead to social isolation, depression and cognitive decline. Even mild hearing loss can also make it difficult to function in situations with background noise.

Aside from hearing loss, operationally tinnitus impacts military mission completion, correlating with sleep disorders, cognitive abnormalities, anxiety, depression, and increased suicide risk, affecting the lives of Veterans both

during and after separation from Service. Even with normal hearing, tinnitus degrades cognition, dichotic listening, and speech-in-noise, an important factor during combat operations where the signal-to-noise ratio is diminished. Those with tinnitus record slower reaction times and poorer accuracy while dual tasking. Sleep disturbance is the second most cited aeromedical factor in Naval Aviation Mishaps and HAZREPS, and 76% of people with tinnitus complain of sleep dysfunction. Sleep degradation is associated with slower reaction time and increased mistakes in recognition of targets as friend or foe (Smith, 2017).

While hearing loss is commonly comorbid with tinnitus, the two disorders appear to have a separate pathophysiologic architecture. Whereas hearing loss appears to emanate from damage to the cochlea, the generation of tinnitus and its perception appears to be associated with areas higher in the brainstem and auditory cortex (Elgoyhen, 2014). Similarly, not all patients with hearing loss suffer from tinnitus, and not all patients with tinnitus suffer from it to the same extent.

While the susceptibility to noise-induced hearing loss differs substantially between individuals, to date we are unable to predict the susceptibility of any given individual to NIHL. Similarly, it is impossible to predict which individuals will suffer from tinnitus following noise exposure, and whether hearing loss induces tinnitus in a given individual.

This manuscript will critically review the current literature addressing genetic susceptibility to NIHL and tinnitus in both human and mouse, ranging from twin studies to genome wide association studies (GWAS) to the phenotypic description of select mouse models. It will then outline possible strategies to identify genetic susceptibility markers - single nucleotide polymorphisms (SNPs) for these disorders, and discuss strengths, pitfalls and strategies to address these challenges.

Sex Differences in Hearing: Probing the Role of Estrogen Signaling

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According to the World Health Organization (March 2018) there are 466 million individuals worldwide with debilitating hearing loss. Alarmingly, an

estimated 1.1 billion young adults are at risk for developing hearing loss due to recreational noise exposure ("Deafness and hearing loss," 2018). Hearing loss is also the second most common health issue (following tinnitus) afflicting military veterans (Yankaskas, 2013). Hearing loss affects both men and women, but importantly, significant sex differences in hearing have been documented in a number of species and are particularly well-documented in humans. Documented differences between the sexes involve both peripheral and central auditory processing, and include cochlear function, the peripheral nerve response to sound in the spiral ganglion, differences in binaural processing, and susceptibility to age-related and noise-induced hearing loss (ARHL and NIHL) (Lichtenhan et al., 2017; McFadden, 2009; Pearson et al., 1995; Szanto & Ionescu, 1983; Zündorf, Karnath, & Lewald, 2011). In addition, a recent study in mice demonstrated differences not only in the susceptibility to noise induced hearing loss (NIHL) between sexes, but also in the response to treatment to prevent NIHL (Milon et al., 2018).

Physiological differences between the sexes are often hormone-driven, and an increasing body of literature demonstrates that the hormone estrogen and its related signaling pathways may in part, modulate the aforementioned differences in hearing between the sexes. Analysis in women with Turner syndrome and women taking hormone replacement therapy provides further evidence of estrogen's role in the modulation of hearing (Hederstierna, Hultcrantz, Collins, & Rosenhall, 2007; Hederstierna, Hultcrantz, & Rosenhall, 2009). At the molecular level, there are two canonical estrogen receptors (estrogen receptor alpha and estrogen receptor beta), both of which are expressed in the ear. Knockout studies in mice have demonstrated that the estrogen receptor beta (ERβ), has a protective effect against acoustic trauma (Meltser et al., 2008). In addition to the two canonical estrogen receptors, a family of estrogen-related receptors and membrane-bound estrogen receptors, a sub-set of which are already known to be expressed in the inner ear, may modulate hearing via genomic and non-genomic pathways (Björnström & Sjöberg, 2005; Jichao Chen & Nathans, 2007; Horard & Vanacker, 2003; Nolan et al., 2013; Tanida, Matsuda, Yamada, Hashimoto, & Kawata, 2015; Vrtačnik, Ostanek, Mencej-Bedrač, & Marc, 2014).

Sex differences in hearing have critical implications for study design, and development of new therapeutics. Currently, there are no approved therapeutics to treat NIHL or ARHL in the human population. Given the large number of individuals worldwide already inflicted by disabling hearing loss, and the even larger at-risk population worldwide, a more complete understanding

of the physiology of hearing will prove invaluable. Subjects from both sexes must be included in all studies for NIHL and these have to be analyzed separately, because of the differential sex-specific response to noise. From a mechanistic perspective, understanding the underpinning of the hormonal modulation of hearing may lead to the development of novel therapeutics for NIHL.

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Inflammatory responses in noise-induced hearing loss: Targets for pharmacological intervention

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Inflammation is a complex biological response to harmful stimuli, which can include infection, tissue damage or toxins. Thus it is not surprising that cochlear damage by noise includes an inflammatory component. One mechanism by which inflammation is generated by tissue damage is the activation of damage-associated molecular patterns (DAMPs). Many of the cellular receptors for DAMPS are also receptors for pathogens, and function in the innate immune system. They include Toll-like receptors (TLRs), NOD-like receptors (NLRs) and DNA receptors. DAMP receptors are known to be expressed by cochlear cells, and binding of molecules released by damaged cells to these receptors would result in the activation of cell stress pathways. This would in turn lead to the generation of pro-inflammatory cytokines and chemokines that recruit pro-inflammatory leukocytes.

There is extensive evidence indicating that pro-inflammatory cytokines including TNF alpha and interleukin 1 beta, and chemokines including CCL2, are induced in the cochlea after noise exposure. The recruitment of macrophages into the cochlea has also been demonstrated. These provide substrates for noise damage to be enhanced by inflammation. Additional evidence is provided by the effectiveness of anti-inflammatory drugs in ameliorating noise-induced hearing loss. Treatment with steroids and anti-TNF medications have both been shown to reduce hearing loss after damaging noise exposure. The involvement of inflammation provides a wide variety of additional anti-inflammatory and pro-resolution agents as potential pharmacological interventions in noise-induced hearing loss.

Both resident cochlear tissue leukocytes and newly recruited mononuclear phagocytes have been demonstrated to participate in cochlear inflammation following noise insult. A pronounced pro-inflammatory activation of resident immune cells in tandem with pro-inflammatory monocytes occurs pursuant to both traumatic noise exposures that precipitate permanent thresholds shifts and chronic exposures to lower-level noise that produce only temporary threshold shifts. That immune activity in the cochlea is triggered even in the event of low-grade noise stresses is indicative of the robust immune capacity of the cochlea following noise exposure.

Extensive research into noise-induced cochlear inflammation has indicated that alterations in cochlear immune homeostasis is a very sensitive

internal sensor for conditions within the cochlear microenvironment. Immune activation occurs in brief succession to noise exposure, and this in turn suggests that changes in immune activity in the cochlea following noise stress has the potential to serve as an early indicator of noise-induced tissue damage. Such an early physiological response may one day be employed as a clinical diagnostic tool in the assessment of noise-induced cochlear damage. What's more, it may provide an impetus for the early administration of pharmacological interventions aimed at either preventing cochlear inflammation or speeding the rate of damage resolution during the healing process—both important future biological targets for remediating and reducing noise-induced inner ear damage.

Circadian Regulation of the Auditory System

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The circadian clock is an evolutionarily highly conserved internal timekeeping mechanism that synchronizes endogenous systems with daily environmental cycles.The mammalian circadian clock is organized hierarchically with the central pacemaker, the suprachiasmatic nucleus (SCN) in the hypothalamus, that orchestrates physiological functions of all peripheral organs (Kalsbeek et al., 2006). Circadian rhythms are innate and are regulated by clock genes. The generation of circadian rhythms involves autoregulatory transcriptional/translational feedback loops (Albrecht, 2002) involving the positive elements CLOCK and BMAL1 that form heterodimers and induce the transcription of the negative-feedback elements *Period* (*Per1* and *Per2*) and *Cryptochrome* (*Cry1* and *Cry2*). The tight coordination of the positive and negative elements of transcription, as well as post-transcriptional and post-translational modifications, impose time delays that produce an accurate cellular oscillator with a 24 h periodicity (Reppert and Weaver, 2002).

Clock transcription factors in tissues coordinate metabolic fuel utilization and storage with alternating periods of feeding and fasting corresponding to the rest-activity cycle. Disruptions in the regulation of circadian rhythms are known to affect a large number of bodily functions including sleep, metabolism and inflammatory responses (Bass and Takahashi, 2010). Cell autonomous clocks are ubiquitously expressed throughout the mammalian body (Yoo et al., 2004). A

robust self-sustained clock was identified in the cochlea. There is ample circadian expression of core clock genes such as *Per1, Per2, Bmal1,* and *Rev-erb* and persistent oscillations of the period2 protein for more than ten days in culture (Meltser et al., 2014). Moreover, PER2 is abundantly expressed in hair cells and spiral ganglion neurons, the primary cells for auditory transmission (Meltser et al., 2014).

A greater sensitivity to night noise trauma was found compared to daytime and coincided with a peak expression of Per2 at night (Meltser et al., 2014). CBA/CaJ mice exposed to a noise trauma (6–12 kHz broadband noise of 100 dB SPL, for 1 h) in the morning (9 am) display complete recovery of their hearing thresholds after two weeks whereas those exposed in the evening (9 pm) still had 10–20 dB hearing threshold shifts, revealing a permanent damage (Meltser et al., 2014). This unexpected permanent threshold shift observed in the night noise exposed group indicates that the auditory system is more vulnerable at night. Investigating the molecular pathways involved in the differential sensitivity to noise-induced hearing loss (NIHL) will increase our knowledge of the mechanisms involving resilience or vulnerability upon noise overexposure at different times of the day.

Not only have we found differential sensitivity to noise trauma but we have also witnessed that some drugs are more effective at nighttime than daytime, whereas for others it's the opposite. This finding suggests that it is not the pharmacodynamics that dictates such outcomes; rather it is the circadian biology of the target cell that will determine whether an organ will respond to a drug at a specific time of the day. These findings are undoubtedly of major relevance for humans since circadian systems in mammalian species are highly homologous and highly conserved. It remains to be determined if alterations in circadian rhythms increase vulnerability to a broad spectrum of auditory insults other than noise trauma (e.g. ototoxic drugs, ischemia). Finally, to fully appreciate the functional significance and the underlying mechanisms we need to know the environmental cues that modulate the cochlear clock. What are the molecular components of the clock machinery that drive vulnerability or resilience to noise? It is also important to know if these effects are auditory-specific, or whether they involve system-wide changes. Addressing these important questions will provide new avenues for understanding the mechanisms underlying auditory damage and optimize preventive and therapeutic interventions adapted in time.

Nutrition and Noise: The Role of Diet in Vulnerability to Noise Injury

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The influence of nutrient intake and diet on successful hearing with age and in mediating protection from challenges such as noise is an important relationship yet to be fully appreciated. Dietary intake creates a stream of effects from providing essential nutrients for basic cellular processes to influencing stress response, immune response, cardidometabolic status, neural status, and psychological well-being. Dietary quality has been shown to alter risk for essentially all chronic health conditions including hearing loss and tinnitus. Evidence of nutrients with antioxidant, anti-inflammatory, anti-ischemic properties and overall healthy diet quality as otoprotective strategies are slowly accumulating, but many questions remain unanswered.

The vast majority of non-human auditory research performed in mammals is done in rodent models, such as mice, rats, guinea pigs, and chinchilla. This is consistent with medical research in general. The omnipresent concern is the translation of animal mode-based findings to humans. Otherwise we are simply describing methods to increase the longevity and fitness of mice. Of course, humans represent a much more complex model in regards to both intrinsic and extrinsic factors. The missing link is understanding and appropriately adjusting for confounding variables in translational research. Most research does not adjust for intrinsic differences in animal models and do not consider extrinsic factors. Diet of course is one of these extrinsic factors. How often have you seen methods sections include description of the dietary intake of animals, consider the nutrient content of their chow, additional food items, record of daily caloric intake? Even if such information is not well described, diet is at least held constant across subjects within studies. As dietary strategies and/or dietary supplements are assessed in humans, there will be a highly variable baseline across participants, which has the potential to influence, or perhaps even confound, human clinical data collection and interpretation of results.

In this review we will discuss 1) the role of nutrition in normal auditory physiology, 2) evidence of nutrient and diet-based otoprotection, and 3) consideration of confounds and limitations to nutrient and dietary study. Unraveling the intricate biochemistry and multitude of interactions of nutrients may ultimately prove infeasible with roughly 60 physiologically essential nutrients and many known synergies and interactions across nutrients, however, it may

also be unnecessary. Various metrics for dietary quality will also be discussed as part of this review.

Longitudinal Hearing Threshold Shifts in US Service Members

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United States military Service Members are routinely exposed to hazardous levels of steady-state and impulse noise. Noise over-exposure can result in permanent damage to structures of the inner ear resulting in permanent sensorineural hearing threshold shifts. Because the normal range of hearing spans from -10 to 20 dB HL, it is entirely possible to have permanent hearing threshold shifts within what is an audiometrically normal hearing range. Despite the permanent hearing changes and damage to the cochlea, these individuals are classified as having normal hearing. Individuals whose hearing thresholds permanently shift beyond about 20 dB HL are in the abnormal hearing range and subsequently labeled as having noise-induced hearing loss (NIHL). Depending on the degree of impairment, a NIHL can be profound, limiting one's ability to hear high frequency sounds, understand speech, and seriously impairing one's ability to communicate. Service Members with NIHL are sometimes unable to perform job duties. Thus, NIHL can affect a Service Members fitness for duty.

There is little information about how slowly or rapidly hearing ability deteriorates at both an individual level as well as at a population level and within different age groups. Furthermore, we know remarkably little about how early noise exposures, including noise exposures which induce permanent hearing shifts but remain within the normal range as well as hearing loss, impact hearing later in life. A deeper understanding of the time course and magnitude

of hearing threshold shifts and the factors which influence the development of hearing threshold shifts will hopefully aid the DoD/VA in designing more effective interventions. Therefore, the aim of the present study is to investigate the decline in Service Members hearing ability over time and the factors influencing this decline.

The Noise Outcomes in Servicemembers Epidemiology Study was designed to examine the longitudinal effects of military and non-military exposures on auditory functioning among post-9/11 Veterans. Individuals are eligible to participate if they are within 2.5 years of military separation (enrollment and follow-up is ongoing). To date, nearly 600 individuals have been enrolled and are being followed prospectively. To determine hearing ability prior to study enrollment, we obtain audiometry monitoring data from the Defense Occupational and Environmental Health Readiness System - Hearing Conservation (DOEHRS-HC) data repository. We currently have monitoring data for the first 350 enrolled NOISE study participants and are in the process of requesting the monitoring data for the remaining enrolled participants. Therefore, this is an historical cohort study design, leveraging audiometric data collected prospectively among Service Members as part of the DoD hearing conservation program.

The outcome variable is hearing threshold level recorded in decibels (dB HL) as measured by a pure-tone audiogram in both the right and left ears at six different frequencies: 500, 1000, 2000, 3000, 4000, 6000 Hz, giving a maximum of 12 observations per visit / per individual. Time between monitoring visits (in years) is the main exposure variable. While the annual rate of change will be determined by frequency, we are further interested in examining how the rates changed due to noise exposure during the military. To this end, we captured noise exposure using a questionnaire developed by the NOISE study. The 18-page Lifetime Exposure to Noise and Solvents Questionnaire (LENS-Q) was designed to obtain a comprehensive, lifetime history of exposure to sources of noise and solvents. Increasing scores on the LENS-Q are associated with increasing noise exposure. For the purposes of this analysis, the LENS-Q will be dichotomized, and Service Members classified as being either exposed to high noise or low noise.

Methods to model the data must account for correlated data, unequal intervals, and missing observations. Therefore, a linear, mixed-effects model will be employed to analyze these longitudinal data. Mixed-effects models allow estimation of the average intercept and rates of change via fixed effects and for individual deviation from the average via estimation of random effects.

Estimation of the random effects is accomplished using all the data available (i.e. all observations for every Service Member will be used in the analysis) and can account for the individual variation in initial threshold and rate of hearing change at each audiometric frequency.

A cursory view of the DOEHRS-HC monitoring data of the first 350 NOISE study participants highlighted the richness of this dataset. There are many repeated observations, averaging 6.6 (range 1 – 22) audiograms for the first 350 Service Members. A total of 11 individuals had only one visit, while 14 individuals had 15 or more visits. Individual empirical growth plots were constructed to view thresholds by audiometric frequency revealing heterogeneity among Service Members hearing shifts over time.

This is a unique use of the DOEHRS-HC data and is the first analysis of hearing shifts over time using such data and will add to the limited literature on the longitudinal effects of hearing.

Trajectory of Noise Induced Occupational Hearing Loss: Potential Times for Intervention

Martin Slade (Yale) and Linda Cantley (Yale)

Approximately 16% of disabling hearing loss in adults globally is attributed to occupational noise and contributes over 4 million disability adjusted life years (DALYs). Within the United States over ten million people are affected by noise induced hearing loss (NIHL), second only to aging as the greatest causes of hearing loss (Alberti, 1998; Lang, 1994). The costs associated with hearing loss include not only a substantial financial burden resulting from workers compensation claims and other insurance costs, but also the myriad but less clearly defined costs associated with quality of life reductions among those with hearing loss. In some instances, hearing impaired workers may require job re-assignment or suffer job loss. Over thirty years ago, the Occupational Safety and Health Administration mandated workplace hearing conservation programs with the purpose of substantially reducing occupational hearing loss (U.S. Department of Labor [USDL], 1983). Since the incorporation of this standard, various approaches have been undertaken to reduce NIHL. These approaches have included the incorporation of engineering controls to reduce the ambient noise levels, requiring the use of various types of hearing protection devices (HPDs), implementing administrative controls that reduce the time employees spend in high noise areas, and employee educational programs for employees

regarding noise exposure and hearing health. Despite these efforts, occupational NIHL remains a significant issue. Moreover, the work environments are getting louder in certain employment sectors. In the United States military, for instance, the increased power required for ever- greater maneuverability of combat aircraft requires a commensurate increase in noise (Aubert & McKinley, 2011).

The disease process of noise induced hearing loss, should be viewed in the context of an individual's social and environmental interactions. Social action theory links social, environmental, and biological influences to the health of the individual through behavioral health theoretical models (Ewart, 1991). As such, social action theory allows epidemiologic studies to incorporate the integration of both biological and behavioral sciences (Cason, 2011). Therefore, noise induced hearing loss can be evaluated not only from the perspective of the biology of cochlea hair cell death, but from behavioral aspects such as the choice of job, use of hearing protection, and overall health and wellness.

Evidence suggests that communication impairments resulting hearing loss can lead to social isolation and increase risk of chronic disease, including depression. Other evidence suggests that hearing loss may affect cognitive load. Under conditions of hearing loss where auditory perception is difficult, greater cognitive resources may be dedicated to auditory perceptual processing to the detriment of other processes such as working memory.

This quantitative study takes advantage of existing longitudinal data encompassing nearly twenty years for a cohort of manufacturing workers from a single corporation. Available data includes individual level demographic information, complete job histories, medical claims and serial audiometric testing results as well as results from industrial hygiene sampling by job. Within this cohort, pure tone audiometric threshold hearing tests were conducted annually for all employees working in jobs where ≥5% of the noise measurement samples equaled or exceeded an 8-hour time-weighted average of 82 dBA.

Hearing threshold was modeled as a function of demographic, occupational, and behavioral factors as well as time, thus creating an adjusted trajectory for hearing threshold levels. Trajectories were determined for the binaural average of each of the measured audiometric frequencies, namely, 500, 1k, 2k, 3k, 4k, 6k and 8k Hz. Additionally, the trajectory of a noise notch, defined as the difference between the average binaural threshold levels at 500, 1k and 8k Hz and the average binaural threshold levels at 3k, 4k and 6k Hz. The trajectory of the noise notch was the primary outcome for the study.

Additionally, the trajectory for the average binaural hearing threshold at 500, 1k, 2k, and 3k Hz was also modeled as this is often the measure associated with hearing impairment for workers compensation purposes.

The study population included 9,262 subjects with an average of 13.5 hearing tests over 13.6 years. The actual number of hearing tests varied from eight to 28 while the range of observation varied between 10.0 and 17.3 years. The subjects were predominately white (85.2%) males (87.9%). Blacks represented 9.4% of the population while Hispanics constituted 4.1% of the cohort. Results and Conclusions will be described in the full-length manuscript.

Section 3: Pre-clinical models currently used to assess novel pharmaceuticals that may prevent NIHL: What are the Strengths and Weaknesses of Current Models and Approaches?

The Mouse as a Model of Cochlear Noise Injury and Related Therapies

Kevin K. Ohlemiller (Washington University School of Medicine)

Laboratory mice have become the primary animal model for understanding of mammalian cochlear function and dysfunction. The mouse cochlea operates according to standard 'mammalian' principles, uses the same cochlear cell types, and exhibits the same types of injury as found in other mammals. Because they are essentially genetically identical, inbred mice provide minimal data scatter and permit smaller sample sizes than might be required for outbred models. Because of ever-advancing tools for gene manipulation, inbred mice also facilitate testing of engineered mutations with minimal effects of unknown modifier genes. As a result, however, any one inbred strain is analogous to a single person. Only by testing a principle or therapy in multiple inbred strains can we discern the central tendency, and how dramatically it may vary across individuals. Although the mouse cochlear spiral is only 5+ mm long, nearly all methods applied to other models can be applied to mice, including behavioral testing, cochlear nerve recording, central auditory recording, and even cochlear perilymph sampling. Newer methods for assaying gene, RNA, and protein expression also work in mice without the need to pool samples. The typical mouse lifespan is packed into less than 3 years, yet the age-associated pathologies that may be found are quite similar to longer-lived mammals. All Schuknecht's types of presbycusis have been identified in existing mouse lines, some favoring hair cell loss while others may favor strial degeneration. Still, few of the over commercial 400 inbred lines have been examined in detail, despite their immense potential for gene discovery.

Mice have drawbacks, including limited access to cochlear scala and rapid metabolism, such that much higher doses of drugs must be given to elicit an effect. Mouse hearing rolls off below ~5 kHz, so that locking of neural impulses to stimulus fine structure (i.e., phase-locking) cannot be easily studied. While no unique anatomic specializations of the mouse cochlea for ultrasonic hearing have been identified, most of the mouse's cochlea is tuned to ultrasonic frequencies. This raises the possibility that some features of mouse cochlear operation may differ from larger mammals. Although noise exposure generally affects the mouse cochlea in a manner similar to other mammals,

species differ with regard to the extent of hair cell loss for a given degree of permanent threshold shift (PTS). Mice appear more prone to non-lethal, but permanent alterations to organ of Corti spatial relationships and hair cell stereocilia. Nevertheless, mice share the rodent characteristic of a fragile cochlea to noise exposure. That is, the amount of noise needed to produce PTS in mice and other rodents is much less than in primates. This suggests that some maintenance and repair processes may differ in type or robustness. In spite of this, creating ototoxic lesions can require prohibitively large doses, or combinations, such as kanamycin plus furosemide to kill hair cells.

Use of mouse models extends to many successful tests of drug therapies, both to preserve and restore hearing. Tested agents have included calcium antagonists, antioxidants, nanoparticles, viral vectors and regulatory RNA. Such studies capitalize on the consistency of mouse data and the economy of mice, although investigators may encounter difficulty in finding effective doses, or determining how these translate to other models. Therapeutic compounds may be applied systemically or locally, by injection through the tympanic membrane into the bulla, or onto (or through) the round window membrane. The thinness of the mouse cochlear capsule and annular ligament may promote drug entry directly from the middle ear, although an extremely active middle ear lining may quickly remove most drugs. Optimal drug application in mice will often require finding ways to target drug application while slowing removal. Preclinical testing of any therapeutic will always require tests in multiple animal models of varying size. Inbred mice can constitute one model providing supporting evidence for any therapeutic, while genetically engineered mice can test hypotheses about receptors and pathways.

The Rat Animal Model for Hearing Science and Noise Exposure

Celia D. Escabi (UT Dallas) & Edward Lobarinas (UT Dallas)

The rat (genus Rattus) is a general term used to refer to larger rodent species with body lengths of five inches or longer. Rats have been historically and unfortunately known as carriers of deadly diseases such as the bubonic plague. As research animals, rats make excellent models for the study of medical, biological, genetic, and behavioral phenomena given their adaptability, robustness, survivability and intelligence. From a management perspective, rats are affordable and relatively easy to maintain. Many strains of rats can reach maturity in three months and females can have up to 12 litters, each with 2 to 22

pups per year (with an average of 8 to 9 pups). Gestation periods are short and last 21-26 days.

With respect to hearing there are both similarities and significant differences between humans and rats. Developmentally, rat hearing matures only after birth whereas the human neonate is able to hear prenatally. This difference makes it possible to study hearing in more ways than would be possible in humans. Objective measures of hearing such as the auditory brainstem response (ABR) can be obtained from rat pups at 12-14 days after birth, opening the opportunity for innovative developmental studies. The frequency range of rat hearing is approximately 0.8-65 kHz with the greatest sensitivity between 8-32 kHz, a range much higher than that found in humans. In contrast, the middle ear mucosa and ossicles are remarkably similar to humans. Like humans, the rat cochlea has approximately 2 ½ turns with a similar arrangement of sensory inner and outer hair cells. The rat central auditory system also shares many anatomical and physiological features that are present in the human auditory system.

The use of rats for hearing research increased in popularity during 1980's primarily for structural and functional studies of the ear. However, it has been less commonly used than guinea pigs, chinchillas and gerbils for studying noise induced hearing loss (NIHL).

In the following sections we present a review of the rat model for NIHL and highlight many of the advancements that have been made using the rat, particularly as these pertain to noise dose, therapeutic drug studies for attenuating NIHL, the hazardous effects of continuous, intermittent, impulse and impact noise and the time course and development of noise induced tinnitus. These studies demonstrate the importance of this animal model for furthering our understanding of the effects of noise on structural, anatomical, physiological, and perceptual aspects of hearing as well as genetic susceptibility to NIHL.

The Guinea Pig as a Model in Studies on Noise Injury and Prevention of Noise Injury

Colleen Le Prell (UTD), Gaëlle Naert (Cilcare), Marie-Pierre Pasdelou (Cilcare)

Guinea pigs (Cavia porcellus) are relatively large (female: 100-900 gram; male: 900-1200 gram) rodents; they are very docile animals that rarely bite or scratch. Their size and friendly, inquisitive nature make them easy to work with in laboratory settings. They are highly social. Female pairs typically can be housed together for social enrichment, but male pairs should be avoided to

reduce the risk of fighting. Male/female pairs are typically to be avoided as guinea pigs can start breeding as early as 4-6 weeks of age. Whereas mice (Mus) and rats (Rattus) are excluded from the protections provided in the 1966 Animal Welfare Act passed by the United States Congress, which is enforced by the US Department of Agriculture (USDA), guinea pigs, hamsters, gerbils, and other rodents are protected species. Protections provided by the AWA increase the USDA inspection requirements for facilities and records related to health and well-being. Regulations vary across countries. In the United Kingdom, for example, the Animals (Scientific Procedures) Act of 1986 protects all rodents.

Guinea pigs have sensitive hearing and good vision, and they communicate using a variety of vocal signals, including, for example, purring, squealing, and whistling. Guinea pigs have been commonly used in studies intended to further our understanding of the auditory system, including both the peripheral and the central components. The human hearing range is typically defined as 20-20,000 Hz whereas the guinea pig hears sounds from 150-50,000 Hz. For humans, hearing is best from about 1000 to 4000 Hz whereas for guinea pigs, hearing is best from 8,000 to 16,000 Hz. Thus, there is a rightward shift of the generally U-shaped audiogram for guinea pigs relative to humans. In addition to widespread use in studies on the normal anatomy and physiology of the auditory system, they have been commonly used in studies assessing the pathological auditory system, after damage induced by noise exposure, ototoxic drug treatment, or other insults. They live approximately 4-8 years, and have thus been less commonly used in studies on age-related hearing loss. The small number of studies conducted on this species reveal age-related changes in hearing as observed in other mammalian species, with higher frequencies showing deficits prior to the development of deficits at lower frequencies.

Guinea pigs can be trained to push buttons or levers when they detect sound, or changes in sound, and thus they have been widely used in psychophysical studies employing behavioral testing. The cochlea and round window are easy to access, making guinea pigs popular for use in studies employing round window based measurements of cochlear nerve discharge, and round window based drug delivery. They have also been relatively widely used in studies that include auditory nerve fiber recordings and the drawing of samples from the cochlear perilymph. The relative ease of access to the cochlea for drug administration and to the auditory nerve has resulted in fairly widespread use of the guinea pig in studies evaluating the pharmacology of the peripheral auditory system, including both ascending excitatory neurotransmitter studies and also descending efferent neurotransmitter studies.

With respect to noise injury, guinea pigs have been used in diverse studies assessing the effects of octave band noise, narrow band noise, impulse noise, blast, etc. Exposure has been acute, intermittent, chronic, etc. It appears to take relatively more noise to damage the guinea pig cochlea relative to the mouse, but relatively less noise than is necessary to damage the rat cochlea. Across rodents, there is an increased vulnerability relative to non-human primates; data from humans are less extensive but humans are also less vulnerable to noise injury than rodents. With respect to the assessment of potential otoprotective agents, as noted above, the round window is easily accessible for direct cochlear therapy. Guinea pigs are also easy to dose via injections, and they have thus been widely used in studies assessing potential otoprotective agents. They have been particularly useful in studies assessing dietary supplements that include vitamin C as one component, as guinea pigs, bats, simian primates (monkeys and apes), and humans are the only mammals that do not synthesize their own vitamin C. This article will review the use of guinea pigs in studies on noise injury, as well as exposed to ototoxic drugs or with age related hearing loss and the use of therapeutics to prevent noise-induced cochlear damage and associated hearing loss.

The Chinchilla Animal Model for Hearing Science and Noise Exposure

Edward Lobarinas (UT Dallas), Monica Trevino (UT Dallas), Amanda Maulden (Purdue University), and Michael Heinz (Purdue University)

The chinchilla, or more specifically the long-tailed chinchilla (Chinchilla lanigera), has been used in hearing science for some time with references dating back to the early 1960's. Chinchillas are indigenous to the Andes Mountains of South America, where they live in herds. The name chinchilla means "little chinchas", a reference to the Chincha people who lived in the same mountain range.

There are a number of benefits to using chinchillas for research related to hearing. First, chinchillas have a frequency range of sensitive hearing that is quite similar to humans (unlike the higher-frequency hearing of mice), and thus are a good model for studies that focus on the effects of hearing loss at frequencies relevant for human auditory perception (e.g., of speech). Second, chinchillas have large heads with relatively easy access to the middle ear and cochlea via an enlarged auditory bulla, which has led to a breadth of published data on issues relevant to conductive and cochlear hearing losses. Third, chinchillas have robust otoacoustic emissions, an indirect measure of outer-hair-

cell function and electromotility. Fourth, chinchillas provide a unique model for understanding the effects of inner-hair-cell dysfunction because, unlike other species where inner-hair-cell dysfunction is typically combined with outer-hair-cell dysfunction, carboplatin can be used to produce selective inner-hair-cell damage in chinchillas. The carboplatin model provides a complement to the selective outer-hair-cell dysfunction models that antibiotics produce in many species (including chinchillas) and the mixed outer- and inner-hair-cell dysfunction models that result from noise exposure. Fifth, furosemide can be used in chinchillas to produce a metabolic model of age-related hearing loss, similar to gerbils and cats. Sixth, the robustness of chinchillas to surgical procedures and anesthesia allows for lengthy (~24-36 hour) neurophysiological single-neuron experiments, which has led to a wealth of detailed single-unit data characterizing responses to both simple and complex sound across the entire peripheral and central auditory system. Seventh, chinchillas have robust and readily measurable auditory evoked potentials at multiple levels of the peripheral and central auditory system. Finally, chinchillas are easy to train and have been used extensively in behavioral detection and discrimination experiments, including pitch and intensity discrimination, noise detection, and localization.

Behaviorally, their docile nature and long life (10-15 years) makes chinchillas suitable for short or long term research. It is important to note that chinchillas are a protected species in the United States via the Animal Welfare Act (AWA) enacted in 1966; provisions to this act are enforced by the Department of Agriculture (USDA). Thus, research using chinchillas is strictly regulated and must be scientifically justifiable over lower species.

Early hearing-science studies on chinchillas focused on temporary and permanent threshold shifts following short- and long-term noise exposures. Many of these experiments assessed changes in hearing using behavioral means, as described in a later paper in this issue. Furthermore, because non-invasive physiological measures provide effective (and more efficient) assays of hearing in chinchillas (e.g., ABR thresholds predict behavioral and auditory-nerve thresholds), many more noise-exposure studies were able to be performed by using physiological assays to characterize hearing losses. The aforementioned characteristics of the chinchilla historically lent themselves well for experiments assessing the effects of duration, bandwidth, and intensity of noise trauma on inner-ear anatomy, physiology, and perception, including studies of binaural versus monaural noise trauma. Among the other parameters of noise, several

studies on chinchillas have aimed at understanding the effect of impulse and impact noise; exposures with direct relevance to occupational noise injury.

Although chinchillas show more susceptibility to traumatic noise exposures, their long history as an animal model of acoustic injury also led to a number of pharmacological rescue and prevention of noise induced hearing loss studies. These studies examined antioxidants and other biologically active compounds and drugs aimed at preventing or limiting the effects of noise trauma.

The overall aim of this paper is to highlight the historical importance of the chinchilla in hearing research related to noise, summarize key findings from the chinchilla animal model as these pertain to noise, and demonstrate the strengths of the model in evaluating, anatomical, behavioral, and physiological changes that occur following temporary or permanent noise induced hearing loss.

Psychophysical Changes in Temporal and Spectral Processing in Chinchillas with Noise-Induced Hearing Loss

Kelly Radziwon, Adam Sheppard, Richard Salvi (State University of New York Buffalo)

The prevalence of noise-induced hearing loss (NIHL) has steadily increased and now affects a large segment of the population. The most common symptom of NIHL is a shift in auditory thresholds, making sounds at the lower end of the dynamic range difficult to detect. However, an important, but often overlooked symptom of NIHL is the degraded ability to resolve temporal, spectral, and amplitude fluctuations in supra-threshold acoustic signals. These abilities are critical for speech perception, especially in difficult listening conditions (Giraudi et al., 1980). The chinchilla has been invaluable in the study of noise induced temporal and spectral processing deficits for several reasons: (1) the chinchilla is audiometrically similar to humans, (2) chinchillas can be readily trained in behavioral tasks, and (3) the shape and size of its skull allows for relatively easy access to the middle ear and cochlea (Miller, 1970). Through a series of studies using the chinchilla model, the Salvi group has elucidated several noise-induced deficits in temporal and spectral processing.

Temporal resolution refers to the minimum amount of time needed to segregate, or resolve, acoustic events (Giraudi-Perry et al., 1982). Since most behaviorally meaningful stimuli, such as animal vocalizations and speech,

fluctuate rapidly in amplitude and frequency over time, a listener's ability to perceive complex signals depends on the ability to resolve changes in the temporal characteristics of sounds (Long, 1994). One of the most widely used assessments of auditory temporal resolution is gap detection. In a typical gap detection task, the listener is trained to detect a brief silent interval, or gap, in an otherwise continuous signal. As the duration of the gap decreases, the amplitude fluctuations in the signal can no longer be resolved and a gap detection threshold can be obtained (Giraudi et al., 1980).

Prior to noise exposure, gap detection thresholds in chinchillas for narrowband noise stimuli presented at 30 dB SL or greater were approximately 3 ms, with thresholds rising to 6 ms for lower level stimuli (Giraudi et al., 1980). Mild acoustic trauma resulting in an approximately 15 dB threshold shift did not impact gap detection thresholds; however, noise exposures inducing threshold shifts of 40 dB or greater resulted in increased gap detection thresholds even when adjusting for hearing loss (Giraudi-Perry et al., 1982). Building on the Giraudi-Perry et al., 1982 study, Salvi and Arehole (1985) found a systematic increase in gap detection thresholds as hearing loss spread progressively from high to low frequencies. In other words, temporal resolution appears to depend not only on the intensity of the noise carrier but also on the audibility of the high frequency components of the test stimuli (Salvi and Arehole, 1985). To examine the underlying neural mechanisms of gap detection in the chinchilla, Zhang et al., 1990 recorded the discharge patterns of auditory nerve fibers to gaps embedded in a broadband noise carrier. They found that the neural recordings closely matched the psychophysical data but were slightly less impacted by the level of the noise stimulus (Zhang et al., 1990). These results, combined with behavioral data, suggest that noise exposure impacting the high frequencies may be particularly detrimental to temporal processing; which can have large implications for understanding speech in the presence of background noise.

In addition to gap detection, another method of assessing temporal resolution is amplitude modulation detection. For this task, a listener is trained to discriminate between an amplitude modulated signal (containing amplitude or frequency perturbation) from unmodulated noise. As the depth of amplitude modulation decreases, and the rate of modulation increases, it becomes more difficult to discriminate the amplitude modulated noise from the unmodulated signal (Salvi et al., 1982b). To determine how high-frequency hearing loss affects amplitude modulation detection, Henderson et al., 1984 exposed chinchillas to a band of high-intensity noise that systematically moved from high to low sound frequencies. As in the gap detection experiments, chinchillas with significant

high-frequency hearing loss had elevated amplitude modulation detection thresholds even when accounting for the level of the noise carrier. These results suggest that the high-frequency regions of the cochlea play an outsized role in auditory temporal resolution (Henderson et al., 1984).

In addition to temporal resolution, frequency resolution (the ability to detect a stimulus at one frequency in the presence of stimuli at different frequencies) is crucial for accurate sound processing (Long, 1994). One of the ways to assess frequency resolution is to obtain thresholds at multiple frequencies in the presence of a constant-level tonal masker. Using this method, the Salvi group conducted a series of experiments comparing behavioral tuning curves with neural evoked-potentials. They found a close correspondence between the two measures, showing the greatest amount of masking at the frequency of the tonal masker. In addition, high-level maskers resulted in an upward spread of masking, i.e., greater masking for probe stimuli above the frequency of the masker (Salvi et al., 1982a, Robertson et al., 1990). Following high-frequency noise exposure, neural tuning curves widened in high-frequency units of the cochlear nucleus (Salvi et al., 1978) and inferior colliculus (Arehole et al., 1989), suggesting a reduced frequency selectivity.

Altogether, these experiments demonstrate the importance of the chinchilla model in developing our understanding of noise-induced deficits in temporal and spectral processing. By correlating neurophysiological responses with psychophysical data before and after noise exposure, the chinchilla model has provided researchers with a greater understanding of psychoacoustic phenomena than could have been achieved by comparing human behavioral data with animal physiological data alone (Zhang et al., 1990).

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The Use of Non-human Primates in Studies on Noise Injury and Prevention of Noise Injury

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A long-standing dogma in audiology has been that outer hair-cells (OHCs) are the most vulnerable elements of the cochlea following acoustic overexposure, particularly because OHC loss corresponds well with elevations in hearing thresholds, and it is readily observable in routine histology. For this reason, the audiogram has been regarded as the gold-standard test for identifying cochlear histopathologies, and it has served as the reference for defining damage-risk criteria in agencies aiming to minimize occupational deafness. Recent animal research has challenged the utility of the audiogram in this regard, demonstrating that a single exposure to moderate noise levels can permanently damage the afferent synapses between inner hair cells (IHCs) and the auditory nerve, while OHCs at frequency-matched places appear unaffected. Because OHCs remain intact, the auditory thresholds are normal in these ears, but 'cochlear synaptopathy' impairs the sound-evoked responses at suprathreshold stimulus levels. Accordingly, cochlear synaptopathy could underlie impairments in speech comprehension observed in some patients with normal audiometric thresholds—the condition referred to as 'Hidden Hearing Loss,' and synaptopathy has been implicated in tinnitus and hyperacusis.

If data from these rodent studies can be directly translated to human occupational exposures, then there is no question that the damage-risk criteria should be adjusted to protect humans from the deleterious effects of cochlear synaptopathy. However, there are several areas where clarification is needed in translation to humans, including the vulnerability of humans to synaptopathy with respect to the sound-pressure level, spectrotemporal characteristics, and duration of the insulting noise. Furthermore, it remains unclear which suprathreshold metric/s (e.g. electrophysiological and/or behavioral), will most robustly estimate the severity of synaptopathy in human cochleas with and without OHC loss and threshold shifts. This is important not only for re-assessing the acoustic exposure limits in the workplace, but also for identifying candidates

eligible for emerging therapies in both academic and industrial domains and for assessing the success or failure of such therapeutics in clinical trials.

The non-human primate may be a key translational model system in many of these regards. Non-human primates occupy a unique niche in biomedical research due to their phylogenetic proximity to humans, and because the physiological processes and phenotypic outcomes associated with human disorders are often closely mirrored in monkey models. Evolutionarily, auditory form and function would be most faithfully represented by chimpanzees and bonobo apes, but practical and ethical considerations exclude the use of apes in biomedical research. Old-world monkeys, such as rhesus macaques, cynomolgus macaques, and baboons, as well as New-World monkeys, such as marmosets and squirrel monkeys, have served as invaluable models in a wide array of biomedical studies, including within the auditory research field. These model systems may be key to better defining regulations and translating therapeutics to humans.

The development of non-human primate models for research into noise-induced hearing loss is in its infancy, but there are important insights gained from the existing work and many questions raised. Here, we will provide a historical review of the non-human primate literature in relation to auditory function, noise exposure, and drug development. We will discuss the advantages and disadvantages of a range of primate model species in terms of anatomical and physiological relevance to humans; housing-, husbandry-, and handling-considerations; and the added regulatory, aesthetic, and ethical concerns associated with using non-human primates in biomedical research in general.

Noise Induced Hearing Loss in Working Canines: Exposure, Injury, and Protection

Peter 'Skip' Scheifele (US Army)

The US Military employs military working dogs (MWDs) as force multipliers. The primary breeds of dogs used as MWDs are the Belgian Malinois and the German Shepherd Dog. Yet, unlike other organizations, the US government has never developed a baseline audiology program adequate to their needs as it applies to noise effects on canine hearing.

Constant noise can have physiologic and psychological effects in several nonhuman species. However, few investigations have focused specifically on the deleterious effects of environmental noise on the auditory system in dogs. Whether constant noise can affect dogs, particularly working dogs that are

relied upon for their enhanced sensory capabilities (e.g. those used in military operations or search and rescue), is important to determine and the conditions or environments that can impair these sensory capabilities need to be well understood.

As a result of the number of cases of congenital deafness in dogs the veterinary and breeding communities have made an extensive effort to have puppies undergo auditory screening between the ages of five (5) to eight (8) weeks of age. The only acceptable audiological test for determining baseline hearing acuity is the Brainstem Auditory Evoked Response (BAER) test. BAER testing can also be used in diagnostic situations and as a baseline for establishing hearing acuity in dogs.

Moreover, although the BAER electrophysiological test is objective in its output (waveforms) the establishment of which peak on the resultant waveforms is subjective with the possible exception of Wave-V and the subsequent trough (VT) of Wave-V. This routine technique that has been used with humans since 1967 (Picton, 2011) and slowly introduced into the animal industry since the 1980's (Kay et al., 1984; Myers et al., 1984; Sims & Moore, 1984; Sims, M., 1988).

Outside of congenital deafness, noise-induced hearing loss (NIHL) is a big factor in kenneled working dogs, those transported in trucks and in helicopters and when exposed to gunfire and explosives. Most occupied military kennels may have peak noise at 110 dB SPL and even require hearing protection of the handlers upon entering. The consequence of NIHL in MWDs is a failure of the dog to properly behave to voice commands and to miss critical acoustic cues while on target in theatre.

Dogs that are routinely deployed to theatre are subject to relatively consistent exposure to noise in the field. This paper will specifically discuss the baseline protocol to be used for audiological testing of military working dogs including BAER and DPOAE (and in some case wideband immittance) and the impacts of gunfire and kennel noise in military kennels on working canine hearing acuity.

Combined blast and concussive impact-induced hearing loss in rats

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Blast exposure-induced trauma has significant clinical consequences that often appear in the form of physical symptoms such as hearing loss and/or tinnitus, headache, dizziness, nausea, double or blurred vision, as well as in the forms of a series of emotional and behavioral symptoms, cognitive problems. Blast exposure consists of primary high-intensity blast shockwaves, secondary injury from blast-propelled debris and shrapnel, and tertiary blast-induced (coup-contrecoup) neurotrauma. Blast trauma, is the leading cause of auditory impairment and traumatic brain injury (TBI) among military personnel and civilians. The high prevalence of blast-induced hearing loss and TBI and their influence on people's quality of life have spurred increased interests for investigating the mechanisms underlying the blast-induced neurological disorders. We have previously reported blast-induced hearing loss. Electrophysiologically, the blast-induced neuronal activity changes in the auditory structures have been used to delineate the neurophysiological mechanisms underlying blast-induced hearing loss. Our studies showed that spontaneous firing rates (SFRs) can be changed in a time-dependent matter in the DCN, IC and AC of blast-exposed animal models. In addition, blast-induced brain damages are known to be associated with diffuse axonal injuries, micro-hemorrhages or vascular anomalies, and glial activation and proliferation. Indeed, glial cells play a significant role in many central homeostatic processes following brain trauma, including actively involved in immunoreactive responses during neuroinflammatory processes. Increased glial activity is one major neuroinflammatory indicator in TBI. Particularly, microglial activation has been suggested to be the key component of inflammatory response in the long term, and such neuronal damage has been found to be correlated with the frequencies of blasts and the degree of neuronal injury worsened with time post-blast. However, it is unknown whether a similar glial reaction exists in the auditory system of rats with tinnitus and related mTBI after the combined blast/impact exposure. In addition to trauma induced blast shock waves alone, the secondary blast impact through concussive impact from explosion-derived debris and shrapnel and blast-shock-wave-propelled acceleration or deceleration of the body often occur. Blast exposure is the major cause of hearing loss and related mild traumatic brain injury (mTBI) in military personnel, which often occurred with the secondary concussive impact with other objects.

However, it is unclear to what degree the blast and concussive impact- contribute to the induced hearing loss and related mTBI, and what the underlying mechanisms. We employed a unique blast-plus-impact animal model by combining blast exposure and concussive impact to reflect the realistic situation where blast is often followed by impact. Our data showed that the hearing thresholds increased throughout all the frequencies at 1 day after blast/impact exposure in the complex TBI animals. The hearing loss was partly recovered at 2 months later as measured by ABR. Similarly, our previous study using blast exposure alone showed the blast exposure has shown to be able to induce the threshold increase in 1 day after blast exposure and at 1 month later the increased threshold recovered partially and maintained at the recovered level for at least 2 month. Although the hearing function was partially recovered, studies showed that animals may have hidden hearing loss, i.e., functional deficits in hearing, which may be result in a decrease in the number of synaptic ribbons in the inner hair cells and spiral ganglion cells and degraded amplitude of ABR wave I. Indeed, our study indicates that the hearing loss at 2 months after blast/impact exposure may have related with the inner and outer hair cells loss in cochlea, which was examined at 2 months after the exposure. The hair cell loss may result in the reduced amplitude of P1 and P5 waveform and P1/P5 ratio in ABR, suggesting the auditory damage in the brain may result from peripheral damage in the peripheral auditory structure. It has been reported that blast shockwaves can cause perforation of the tympanic membrane, disrupt the organ of Corti, and induce hair cell loss, which in turn triggers loss of spiral ganglion neurons and the degenerative processes in the central auditory pathways. We consider that the hearing loss is more likely due to the damage induced by blast as shown in our previous study using blast or noise exposure alone due to the fact that the blast-exposed ear has different threshold from the non-blast-exposed ear. Although concussive impact may play a minor effect on hearing loss, concussive impact adversely affect the whole brain functions, including auditory functions. The concussive impact due to shrapnel and debris from blasts, especially those do not penetrate the skull or brain, may adversely affect brain functions. Such impact may occur at both the peripheral and central levels.

In addition to the regulatory effects on the neurons, glial cells, especially microglial cells, are the immune effector cells in the central nervous system and accumulate at the site of injury and play a neuroprotective role phagocytosing damaged cells and debris following a damaging event. Although increased glial activity was observed at a short-term after traumatic injury in the cortex of rats, the long-term effect and the effect in auditory structure at a long-term after brain injury has not been reported before, except that the long-term neuroinflammatory response was found in the neurodegenerative disorders in human after brain trauma. Thus, it is vital to study the long-term neuroinflammatory reaction in the central auditory system in repetitive blast exposure and concussive impact-induced TBI animal model. Interestingly, our data showed higher microglial reactivity in the DCN ipsilateral to the blast-exposed ear and in the IC and AC contralateral to the blast-exposed ear as compared to the non-blast exposed ear. Such patterns apparently reflect the fact that the auditory ascending nerve fibers in the DCN predominantly project to the contralateral IC and AC, compared to their opposite counterpart structures. Our results suggest that blast exposure triggered neuroinflammatory reaction, which progressed along the ascending projections in the central auditory system. It also suggests that the neuroinflammation reaction in the auditory system may, at least partially, contribute to hearing loss, tinnitus or hyperacusis in blast exposure-induced TBI. Moreover, concussive impact increases microglial activity, which has been observed through the cortex at the epicenter of concussion injury. Our current study further demonstrated that the increased microglial activity also exist in the auditory system. When comparing the side of auditory structures that were not affected by blast with that of sham controls, we found higher microglial activity especially in the auditory brainstem. This suggests that concussive impact alone may have directly initiated neuroinflammatory processes in the auditory centers, which may also play a role in blast/impact-induced TBI symptoms or disorders. Indeed, it has been reported that blunt trauma of the head may lead to auditory dysfunction, including tinnitus, hyperacusis and hearing loss. Chronic glial activity can persist for weeks to months after experimental concussive-like injuries. Moreover, the concussive effects on the auditory structures in this study may also come from the brain injury induced by blast wave injury. An animal model with weight drop injury

alone, without the shock wave injury, would provide more evidence of the neuroinflammatory reaction in the central auditory system.

In summary, blast or concussive impact rare occurs alone, especially in military settings and multiple incidents often occur. Based on our results from TBI animal model with tinnitus and hearing loss, it is suggested that tinnitus may due to severe hair cell damage, decreased neuronal activity changes and increased anti-inflammatory microglial activity. Although neuronal hyperactivity has been suggested as a potential mechanism underlying tinnitus and hearing loss, our results suggest that neuronal hypoactivity also may play an important role. In addition, neuroinflammation in the auditory centers may play an important role in the etiology of chronic tinnitus, hearing impairment, other brain injuries. Although microglial cell reactivity is a well-known indicator for inflammation reaction, TBI is known to trigger inflammatory pathways, in part, by increasing the levels of cytokines and chemokines. Thus, further study on interleukin-1 beta (IL-1β) and tumor necrosis factor alpha (TNF-α) levels would beneficial for understanding further the neuroinflammatory reaction in auditory damages induced by blast and impact. In addition, besides the auditory structures, other brain structures such as hippocampus or limbic structures may also be involved in the etiology of tinnitus and worth further investigation. The mechanisms underlying tinnitus and hearing loss induced by blast/impact and the relationship between hearing loss in and tinnitus in the repetitive TBI model needs further investigation. Our findings confirm the development of neuropathological changes due to blast and concussive impact exposure. The activation of microglia and other cell types potentially involved in inflammatory processes or neuronal activities are important areas for future study.

Pharmaceutical otoprotection strategies to prevent impulse noise-induced hearing loss

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Pharmaceutical otoprotection from noise-induced hearing loss (NIHL) has been a major topic of research for well over two decades. Among the many

challenges associated with pharmaceutical otoprotection from NIHL is the heterogeneity of the acoustic properties of the noise exposures and the subsequent heterogeneity in the cochlear injuries that can result. Impulse noises result from the abrupt release of energy into the atmosphere (Hamernik and Hsueh, 1991), with the most common cause being gunfire. Acoustically, the impulses will vary considerably depending on the source and the propagation medium, but as damaging noise sources, they are characterized by their short durations and high speak sound pressure levels (SPLs). Transient exposures, whether they are impulses and impacts (resulting from the collision of objects), induce a broad set of pathologies to the cell populations in the cochlea that present unique challenges for pharmaceutical otoprotection.

When considered as a damaging noise exposure, impulse exposures vary depending on the peak SPL, the number of impulses in the exposure, and the rate of presentation of the impulses. These variables will contribute heavily to the magnitude of the cochlear injury, the resulting temporary (TTS) and permanent (PTS) threshold shifts, and the types pathologies that occur in the cochlea. Of particular concern when considering protection strategies is the relative contribution of mechanical versus metabolic injury. Impulse exposures have been documented to cause significant degrees of mechanical injury to the cochlea, including: shearing of the reticular lamina causing leakage of the endolymph into the compartments filled with cortilymph (Geyer et al., 1978), loss of the mooring of the basilar membrane to the modiolus, disconnection of Hensen's and Deiters' cells (Hamernik et al., 1984), stereocilia damage (Slepecky et al., 1981), and detachment of the outer hair cells (OHCs) from the Deiters' cells (Henderson et al., 2006). These mechanical injuries have several consequences to cochlear physiology and hearing loss. Acutely, they can result in threshold shift due to reduced cochlear amplification and mechanical transduction efficacy. Further, they can trigger longer-term metabolic damage, including oxidative stress (Xiong et al., 2011), inflammation (Kirkegaard et al., 2006), and dysfunction of the mitochondria (Hu, 2007). The combined mechanical and metabolic injuries from impulse noise act as triggers for apoptotic and necrotic cell death (Hu et al., 2006).

From the perspective of pharmaceutical otoprotection, the focus is largely on prevention of metabolic cell death. Reducing the mechanical trauma to the cell populations requires acoustic protection measures that limit the amount of air and bone conducted energy to the cochlea. The goal of pharmaceutical protection is to preserve as many of the cochlear cells as

possible after the mechanical trauma. Preservation of cochlear cells will reduce loss of function in the acute phase after the exposure, or will permit a restoration of as much function as possible in the chronic recovery phase after the exposure. Prevention of injury will manifest in reduced compound threshold shift in the acute period after the exposure, and restoration of function will result in a larger recovery of thresholds (shifting more of the threshold shift from PTS to TTS). While the preservation of cells in the cochlea does not guarantee restoration of function after mechanical disruption, death of hair cells or spiral ganglion neurons in the cochlea will limit the amount of recovery that is possible.

While many occupational NIHLs occur gradually over periods of months or years, the transient nature of impulse noise creates a different time course for injury and intervention. In cases of single, high-level impulse exposures, hair cell injury and death occur over a window of time that can extend through 30 days after the exposure (Hamernik et al., 1984). This 30-day window allows for post-exposure rescue treatments aimed at maximizing recovery. As the impulse presentation rate (in impulses/sec) increases, the peak SPL decreases, and/or the number of exposures increases, it is reasonable to expect that the pattern of injury would start to resemble a standard occupational exposure more closely. This, in turn, would minimize opportunities for post-exposure rescue. For the purposes of this review, the focus will be on otoprotection (prevention and rescue) from impulse exposures that were designed to evoke combinations of mechanical and metabolic injuries. Successful otoprotection from impulse NIHL has been demonstrated across several animals and exposure paradigms for five primary classifications of compounds, each of which will be discussed separately: 1) Magnesium supplements, 2) Antioxidants, 3) Anti-inflammatories, 4) Glutamate receptor antagonists, 5) Anti-apoptotic compounds. The compounds will be used to group the experiments together, but critical attention will be paid to acoustic properties of the impulse exposures to provide consideration to the influence that the exposures may have on the otoprotection results that were obtained in the experiments.

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Octave Band Noise Exposure: Laboratory Models and Otoprotection Efforts

Colleen Le Prell (UT Dallas), Sarah Gittleman (UT Dallas), and Tanisha Hammill (DoD HCE)

Hammill (2017) completed a systematic review of the literature on pharmaceutical interventions for hearing loss. Publications that reported findings from original reports of pre-clinical animal or human controlled trials of chemical interventions to prevent or treat hearing loss or peripheral tinnitus caused by noise or blast exposure in any setting were included, with an initial search return of 3,492 articles. After excluding duplicate articles, studies that did not assess interventions for noise-induced hearing loss or noise-induced tinnitus, studies that assessed anything other than chemical agents, studies that did not use in vivo methods, studies on regeneration, etc., a total of 213 studies published in 80 unique journals between 1977 and 2016 remained. These 213 articles were inserted into a database shared with the Department of Defense

(DOD) Hearing Center of Excellence (HCE) Pharmaceutical Interventions for Hearing Loss (PIHL) Working Group Members. The initial sections of this manuscript will describe the methods used for the systematic review in detail.

The Hammill (2017) database specifically included complete reference information, noise exposure parameters, species, and intervention. The primary analyses of the database were descriptive, including species, sex, exposure type, measurement utilized, drug, and drug administration protocol. We have expanded the database to include frequency-specific threshold shift measured in control animals (i.e., in the absence of pharmaceutical intervention) across studies. In this report, we will describe specific patterns of hearing loss as a function of species and noise exposure parameters to facilitate the selection of appropriate pre-clinical models in future pre-clinical drug development efforts. The emphasis of this report is octave band noise exposure, as this is one of the most common exposure protocols across pharmacological otoprotection studies; however, hearing loss induced by octave band exposure will be contrasted with hearing loss induced by other exposures.

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Hammill, T. L. (2017). An Evidence-base and Implementation Framework for Promoting Best Practices in Pharmaceutical Interventions for Hearing Loss (PIHL) Research. Dissertation, University of Texas at Austin

The use of pure tones, narrow and broad band noise as traumatic stimuli in hearing research

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Introduction

Intact and highly sensitive hearing is essential for the soldier. It is also the most fragile sensory organ which is very sensitive to damage following occupational exposure to noise. Hearing loss and tinnitus are the two most prevalent health issues for veterans, which result from trauma to the inner ear. Trauma can arise from chronic noise exposure over years of service or brief exposure to high levels of noise, such as a blast wave injury or repeated

exposure over the course of hours. The effect of noise on hearing leads to a continuum of issues. Milder noise exposures lead to hidden hearing loss, associated with a decreased ability to detect sound in the presence of competing noise. More intense noise exposure can lead from temporary auditory threshold shifts lasting days, to permanent threshold shifts. These conditions constitute noise induced hearing loss (NIHL). To date, there are no cures for noise-induced hearing loss and tinnitus in humans.

Statement of problem

Noise-induced trauma in laboratory animals is the primary model for studying NIHL. Unfortunately, there is limited consensus with regard to experimental design for NIHL studies. Differences in protocol, species, and strain of animal can significantly affect the intensity of trauma required to produce a quantifiable change in the behavioral, physiological, or molecular indicator of NIHL. In addition, methods sections often the lack a detailed, accurate description of the stimulus parameters employed to induce trauma. Each of these factors can greatly affect reproducibility of the study; reproducibility of animal studies is essential for translation to humans.

Methods

We conducted a review of the NIHL literature, focusing primarily on studies published between 2007 and 2018. PubMed was the database used to identify papers, using the search terms “noise-induced hearing loss,” “noise trauma,” and “tone trauma.” Papers were excluded if the study addressed an issue that was not hearing related.

Results

Our review identified significant variability in experimental design. While the following were often not reported, when these details were included in the publication we found variability in 1) the time of day the experiment was conducted, 2) the type of anesthetic used if the study did not occur in awake animals (as most anesthetics are otoprotectants), and 3) the stimulus parameters used to induce trauma. A very critical aspect of induction of trauma includes the stimulus parameters used to induce NIHL. These important parameters include bandwidth, level, and duration. With regard to bandwidth, a pre-computed waveform allows for a well-defined spectrum (including infinitely sharp edges to the noise band) whereas noise filtered by the hardware is less well defined. Since sharp changes in audiograms have been correlated with the presence of tinnitus in humans, pre-computed versus filtered noise as a

traumatizing stimulus can lead to significant differences in NIHL or tinnitus. Sound trauma level was in some reports defined by its peak level, while in other reports by its mean level. More importantly, numerous studies failed to report the reference sound level used to define trauma level. Since OSHA guidelines indicate that a main determinant of whether noise will lead to hearing impairment is the exposure occurring within a 24 hour period, reports should also include a description of the temporal characteristics of the traumatizing stimulus, which was not reported in a number of studies.

Conclusion

As a result of our review, we suggest that the aspects of experimental design described above are among the more critical parameters needing to be included in studies on NIHL. We recommend that investigators report and define these parameters in order to optimize the reproducibility of studies on NIHL. Establishing a consensus for study parameters for inducing NIHL would greatly advance research in NIHL.

Section 4: Guidance for Translation

Overarching Challenges in the Development of Pharmaceutical Interventions for Hearing Loss

Colleen Le Prell (UT Dallas), JR Stefanson (DoD HCE), Tanisha Hammill (DoD HCE)

The final paper in this special edition will include a short review of the issues that were raised by the contributing authors. Efforts will be made to tie discussions of species and pre-clinical noise exposure models to parallel discussions of human populations and real-world settings in which noise injury is possible. The feasibility of implementing recommendations for use of theoretical FDA-approved products will be considered, and potential costs and barriers to adoption will be briefly reviewed. At this time, there are no FDA-approved therapeutics for the prevention of noise-induced hearing loss, or other forms of acquired hearing loss. Multiple labs and commercial enterprises hope this will one day change; this article will offer thoughts on the roadmap to approval.

RECENTLY PUBLISHED LITERATURE

Articles determined to be of particular interest will be listed with full abstract in "Research Highlights" below, followed by the remainder of the "Relevant Literature," all published between January 2018 (the end of the last Newsletter search term) and August 2018.

RESEARCH HIGHLIGHTS

Editors evaluated over 337 article abstracts and full text articles as needed for inclusion in this edition's listing of recently published PIHL-related literature. While the final retention of articles was a subjective decision by the editors, care was taken to ensure that articles met at least a basic criterion of relevance or interest to the PIHL community, with a focus on interests of the Noise Committee. Articles which examined the effects of noise on the auditory system, protection from noise, and pharmaceutical interventions for mitigating noise-induced hearing injuries were retained. Select studies with relevance to PIHL-related population selection or study design implications have also been included.

Searching only PubMed, the following search was conducted: "Noise-induced hearing loss" or "noise-induced hearing loss" and "pharmaceutical" or "noise" and "hearing loss" or "noise" and "hearing loss" and "pharmaceutical" or "otoprotection" or "noise" and "otoprotection" or "hearing loss" and "otoprotection" or "acoustic injury" and "noise" or "acoustic damage" and "noise" or "auditory injury" and "noise" or "auditory damage" and "noise": 337 articles reviewed by abstract; 156 selected, 33 abstracts highlighted below. The omitted articles were either unrelated to auditory effects of noise, or assessed non-pharmaceutical interventions.

Inner Ear Hair Cell Protection in Mammals against the Noise-Induced Cochlear Damage.
Waqas M, Gao S, Iram-Us-Salam, Ali MK, Ma Y, Li W.
Neural Plast. 2018 Jul 15;2018:3170801. doi: 10.1155/2018/3170801. eCollection 2018.

Inner ear hair cells are mechanosensory receptors that perceive mechanical sound and help to decode the sound in order to understand spoken language. Exposure to intense noise may result in the damage to the inner ear hair cells, causing noise-induced hearing loss (NIHL). Particularly, the outer hair cells are the first and the most affected cells in NIHL. After acoustic trauma, hair cells lose their structural integrity and initiate a self-deterioration process due to the oxidative stress. The activation of different cellular death pathways leads to complete hair cell death. This review specifically presents the current understanding of the mechanism exists behind the loss of inner ear hair cell in the auditory portion after noise-induced trauma. The article also explains the recent hair cell protection strategies to prevent the damage and restore hearing function in mammals.

Small Arms Fire-like noise: Effects on Hearing Loss, Gap Detection and the Influence of Preventive Treatment.
Altschuler RA, Halsey K, Kanicki A, Martin C, Prieskorn D, DeRemer S, Dolan DF. Neuroscience. 2018 Jul 25. pii: S0306-4522(18)30502-5. doi: 10.1016/j.neuroscience.2018.07.027. [Epub ahead of print]

A noise-induced loss of inner hair cell (IHC) - auditory nerve synaptic connections has been suggested as a factor that can trigger the progression of maladaptive plastic changes leading to noise-induced tinnitus. The present study used a military relevant small arms fire (SAF)-like noise (50 biphasic impulses over 2.5 min at 152 dB SPL given unilaterally to the right ear) to induce loss (~1/3) of IHC synaptic ribbons (associated with synapse loss) in rat cochleae with only minor (less than 10%) loss of outer hair cells. Approximately half of the noise-exposed rats showed poorer Gap Detection post-noise, a behavioral indication suggesting the presence of tinnitus. There was significantly greater loss of IHC ribbons in noise-exposed rats with reduced Gap Detection compared to noise-exposed rats retaining normal Gap Detection. We have previously shown systemic administration of piribedil, memantine, and/or ACEMg significantly reduced loss of IHC ribbons induced by a 3 h 4 kHz octave band 117 dB (SPL) noise. The present study examined if this treatment would also reduce ribbon loss from the SAF-like noise exposure and if this would prevent the reduced Gap Detection. As in the previous study, piribedil, memantine, and ACEMg treatment significantly reduced the noise-induced loss of ribbons, such that it was no longer significantly different from normal. However, it did not prevent

development of the reduced Gap Detection indication of tinnitus in all treated noise-exposed rats, reducing the incidence but not reaching significance.

The protective effect of adrenocorticotropic hormone treatment against noise-induced hearing loss.
Mutlu A, Ocal FCA, Erbek S, Ozluoglu L.
Auris Nasus Larynx. 2018 Oct;45(5):929-935. doi: 10.1016/j.anl.2017.12.006. Epub 2018 May 7

OBJECTIVE:
NIHL is a common problem, and steroids are the most effective treatment option. In this study, we aimed to evaluate the protective effects of the synthetic adrenocorticotropic hormone (ACTH) analogues, which induce endogenous steroid secretion, against noise-induced hearing loss (NIHL) and to compare their effectiveness with that of steroid treatment.
METHODS:
Twenty-four male Sprague-Dawley albino rats were divided into four subgroups as follows: group 1 (n=6) control, group 2 (n=6) saline, group 3 (n=6) dexamethasone (2mg/kg/day intramuscularly [IM]), group 4 (n=6) ACTH analogue (0,4mg/kg/day IM), respectively. Three groups (groups 2-4) were exposed to white noise (105dB SPL, 12h). All the rats were evaluated for hearing thresholds of 10kHz, 20kHz, and 32kHz via acoustic brainstem responses (ABR) measurement. After the basal threshold measurements, measurements were repeated immediately after the noise and on day 7 and day 21.
RESULTS:
Both steroid and ACTH analogue groups showed significantly better hearing outcomes than the saline group on day 7 ($p<0.001$) and day 21 ($p<0.001$) after the noise exposure. No superior treatment effect was demonstrated in either the steroid or ACTH analogue group. None of the related intervention groups reached the basal hearing thresholds.
CONCLUSION:
Steroids were effective drugs for the treatment of NIHL. ACTH analogues also demonstrated promising therapeutic effects for NIHL. Further studies to establish ACTH analogues as an alternative NIHL treatment option to steroids are needed.

Blast-induced cochlear synaptopathy in chinchillas.
Hickman TT, Smalt C, Bobrow J, Quatieri T, Liberman MC.
Sci Rep. 2018 Jul 16;8(1):10740. doi: 10.1038/s41598-018-28924-7

When exposed to continuous high-level noise, cochlear neurons are more susceptible to damage than hair cells (HCs): exposures causing temporary threshold shifts (TTS) without permanent HC damage can destroy ribbon synapses, permanently silencing the cochlear neurons they formerly activated. While this "hidden hearing loss" has little effect on thresholds in quiet, the neural degeneration degrades hearing in noise and may be an important elicitor of tinnitus. Similar sensory pathologies are seen after blast injury, even if permanent threshold shift (PTS) is minimal. We hypothesized that, as for continuous-noise, blasts causing only TTS can also produce cochlear synaptopathy with minimal HC loss. To test this, we customized a shock tube design to generate explosive-like impulses, exposed anesthetized chinchillas to blasts with peak pressures from 160-175 dB SPL, and examined the resultant cochlear dysfunction and histopathology. We found exposures that cause large >40 dB TTS with minimal PTS or HC loss often cause synapse loss of 20-45%. While synaptopathic continuous-noise exposures can affect large areas of the cochlea, blast-induced synaptopathy was more focal, with localized damage foci in midcochlear and basal regions. These results clarify the pathology underlying blast-induced sensory dysfunction, and suggest possible links between blast injury, hidden hearing loss, and tinnitus.

Effects of lifetime noise exposure on the middle-age human auditory brainstem response, tinnitus and speech-in-noise intelligibility.
Valderrama JT, Beach EF, Yeend I, Sharma M, Van Dun B, Dillon H.
Hear Res. 2018 Aug;365:36-48. doi: 10.1016/j.heares.2018.06.003. Epub 2018 Jun 12

Recent animal studies have shown that the synapses between inner hair cells and the dendrites of the spiral ganglion cells they innervate are the elements in the cochlea most vulnerable to excessive noise exposure. Particularly in rodents, several studies have concluded that exposure to high level octave-band noise for 2 h leads to an irreversible loss of around 50% of synaptic ribbons, leaving audiometric hearing thresholds unaltered. Cochlear synaptopathy following noise exposure is hypothesized to degrade the neural encoding of sounds at the subcortical level, which would help explain certain listening-in-noise difficulties reported by some subjects with otherwise 'normal' hearing. In response to this peripheral damage, increased gain of central stages of the auditory system has been observed across several species of mammals, particularly in association with tinnitus. The auditory brainstem response (ABR) wave I amplitude and waves I-V amplitude ratio have been suggested as non-invasive indicators of

cochlear synaptopathy and central gain activation respectively, but the evidence for these hearing disorders in humans is inconclusive. In this study, we evaluated the influence of lifetime noise exposure (LNE) on the human ABR and on speech-in-noise intelligibility performance in a large cohort of adults aged 29 to 55. Despite large inter-subject variability, results showed a moderate, but statistically significant, negative correlation between the ABR wave I amplitude and LNE, consistent with cochlear synaptopathy. The results also showed (a) that central gain mechanisms observed in animal studies might also occur in humans, in which higher stages of the auditory pathway appear to compensate for reduced input from the cochlea; (b) that tinnitus was associated with activation of central gain mechanisms; (c) that relevant cognitive and subcortical factors influence speech-in-noise intelligibility, in particular, longer ABR waves I-V interpeak latencies were associated with poorer performance in understanding speech in noise when central gain mechanisms were active; and (d) absence of a significant relationship between LNE and tinnitus, central gain activation or speech-in-noise performance. Although this study supports the possible existence of cochlear synaptopathy in humans, the great degree of variability, the lack of uniformity in central gain activation and the significant involvement of attention in speech-in-noise performance suggests that noise-induced cochlear synaptopathy is, at most, one of several factors that play a role in humans' speech-in-noise performance.

Cochlear hair cell regeneration: an emerging opportunity to cure noise-induced sensorineural hearing loss.
Youm I, Li W.
Drug Discov Today. 2018 Aug;23(8):1564-1569. doi: 10.1016/j.drudis.2018.05.001. Epub 2018 May 4.

In mammals, cochlear hair cells have a pivotal role in transducing mechanical energy into electrical signals. Cochlear hair cells are sensitive to acoustic trauma, drug insults, aging, and environmental or genetic influences that can cause permanent hearing loss. Currently, many researchers have focused on noise-induced sensorineural hearing loss (SNHL). Noise-induced SNHL is primarily caused by damage to hair cells of the cochlear sensory epithelium. Here, we summarize recent progress in restoring the sensory epithelium after SNHL resulting from noise exposure. The prevalent strategy to regenerate cochlear hair cells is through transdifferentiation of the supporting cells via the inhibition of the NOTCH 1 pathway.

Noise exposure and auditory thresholds of military musicians: a follow up study.
Müller R, Schneider J.
J Occup Med Toxicol. 2018 Apr 12;13:14. doi: 10.1186/s12995-018-0196-7. eCollection 2018.
Background:
Military musicians are working in a noisy environment with high sound exposure levels above the international standards. Aim of the current study is to find out, whether they develop the expected hearing impairments. Adherence to the regulations for prevention in musicians is more difficult than in other occupational fields.
Methods:
In an interval of 13.3 years, 36 out of 58 male military musicians of a German army music corps were subjected twice to an audiometric audit. There were no exclusion criteria apart from acute ENT infections (three musicians). These results were compared with one another and evaluated by means of statistical methods for relationships with several factors.
Results:
At frequencies below 3 kHz, the follow-up audiograms were up to 5 dB better than the preliminary examination. From 4 kHz up to 8 kHz the preliminary investigations showed less hearing impairment. Averaging all frequencies the improvement of hearing ability was around 1 dB. Above 1 kHz the average hearing of the right ear was up to 7 dB better than that of the left ear. Age-induced hearing loss was 3 to 8 dB lower than predicted by ISO standards over the entire frequency range. The side of the ear (right/left) and the frequency (3, 4, and 6 kHz) were significant ($p < 0.05$) in hearing loss, whereas the influence of the instrument and the acoustic traumata were not.
Conclusion:
Despite the high noise levels, the average hearing ability of the 36 military musicians during the investigation period only slightly deteriorated in the noise-sensitive frequencies (3, 5 and 6 kHz). Music may be less harmful than industrial noise, or the long-term auditory training of the musicians leads to a delayed presbycusis.

Hearing vulnerability after noise exposure in a mouse model of reactive oxygen species overproduction.
Morioka S, Sakaguchi H, Yamaguchi T, Ninoyu Y, Mohri H, Nakamura T, Hisa Y, Ogita K, Saito N, Ueyama T.
J Neurochem. 2018 Aug;146(4):459-473. doi: 10.1111/jnc.14451. Epub 2018 Jul 23.

Previous studies have convincingly argued that reactive oxygen species (ROS) contribute to the development of several major types of sensorineural hearing loss, such as noise-induced hearing loss (NIHL), drug-induced hearing loss, and age-related hearing loss. However, the underlying molecular mechanisms induced by ROS in these pathologies remain unclear. To resolve this issue, we established an in vivo model of ROS overproduction by generating a transgenic (TG) mouse line expressing the human NADPH oxidase 4 (NOX4, NOX4-TG mice), which is a constitutively active ROS-producing enzyme that does not require stimulation or an activator. Overproduction of ROS was detected at the cochlea of the inner ear in NOX4-TG mice, but they showed normal hearing function under baseline conditions. However, they demonstrated hearing function vulnerability, especially at high-frequency sounds, upon exposure to intense noise, which was accompanied by loss of cochlear outer hair cells (OHCs). The vulnerability to loss of hearing function and OHCs was rescued by treatment with the antioxidant Tempol. Additionally, we found increased protein levels of the heat-shock protein 47 (HSP47) in models using HEK293 cells, including H_2 O_2 treatment and cells with stable and transient expression of NOX4. Furthermore, the up-regulated levels of Hsp47 were observed in both the cochlea and heart of NOX4-TG mice. Thus, antioxidant therapy is a promising approach for the treatment of NIHL. Hsp47 may be an endogenous antioxidant factor, compensating for the chronic ROS overexposure in vivo, and counteracting ROS-related hearing loss.

A novel nanoparticle delivery system for targeted therapy of noise-induced hearing loss.
Kayyali MN, Wooltorton JRA, Ramsey AJ, Lin M, Chao TN, Tsourkas A, O'Malley BW Jr, Li D.
J Control Release. 2018 Jun 10;279:243-250. doi: 10.1016/j.jconrel.2018.04.028. Epub 2018 Apr 16.

Hearing loss is the most prevalent sensory disability worldwide and may be caused by age, drugs or exposure to excessive noise. We have previously developed a minimally-invasive nanohydrogel drug delivery system that successfully delivers nanoparticles into the inner ear. We have substantially extended this technique by functionalizing the nanoparticles and introducing a targeting peptide which recognizes prestin, a transmembrane electromotile protein uniquely expressed in outer hair cells (OHCs) of the inner ear. We demonstrate the successful delivery of molecules and plasmids specifically to OHCs. When compared to untargeted nanoparticles, the delivery of a c-Jun N-

terminal kinase (JNK) inhibitor, D-JNKi-1, to OHCs by targeted nanoparticles improved protection from noise induced hearing loss (NIHL). This is the first demonstration of a protection from NIHL using a novel safe and controllable delivery system which is minimally-invasive to the inner ear and, as such, is an extremely appealing technique for use in many clinical applications.

Impaired speech perception in noise with a normal audiogram: No evidence for cochlear synaptopathy and no relation to lifetime noise exposure.
Guest H, Munro KJ, Prendergast G, Millman RE, Plack CJ.
Hear Res. 2018 Jul;364:142-151. doi: 10.1016/j.heares.2018.03.008. Epub 2018 Mar 9.

In rodents, noise exposure can destroy synapses between inner hair cells and auditory nerve fibers ("cochlear synaptopathy") without causing hair cell loss. Noise-induced cochlear synaptopathy usually leaves cochlear thresholds unaltered, but is associated with long-term reductions in auditory brainstem response (ABR) amplitudes at medium-to-high sound levels. This pathophysiology has been suggested to degrade speech perception in noise (SPiN), perhaps explaining why SPiN ability varies so widely among audiometrically normal humans. The present study is the first to test for evidence of cochlear synaptopathy in humans with significant SPiN impairment. Individuals were recruited on the basis of self-reported SPiN difficulties and normal pure tone audiometric thresholds. Performance on a listening task identified a subset with "verified" SPiN impairment. This group was matched with controls on the basis of age, sex, and audiometric thresholds up to 14 kHz. ABRs and envelope-following responses (EFRs) were recorded at high stimulus levels, yielding both raw amplitude measures and within-subject difference measures. Past exposure to high sound levels was assessed by detailed structured interview. Impaired SPiN was not associated with greater lifetime noise exposure, nor with any electrophysiological measure. It is conceivable that retrospective self-report cannot reliably capture noise exposure, and that ABRs and EFRs offer limited sensitivity to synaptopathy in humans. Nevertheless, the results do not support the notion that noise-induced synaptopathy is a significant etiology of SPiN impairment with normal audiometric thresholds. It may be that synaptopathy alone does not have significant perceptual consequences, or is not widespread in humans with normal audiograms.

Effects of parenteral papaverine and piracetam administration on cochlea following acoustic trauma.

Kum NY, Yilmaz YF, Gurgen SG, Kum RO, Ozcan M, Unal A.
Noise Health. 2018 Mar-Apr;20(93):47-52. doi: 10.4103/nah.NAH_31_17.
Introduction:
Noise exposure, the main cause of hearing loss in countries with lot of industries, may result both in temporary or permanent hearing loss. The goal of this study was to investigate the effects of parenteral papaverine and piracetam administration following an acoustic trauma on hearing function with histopathologic correlation.
Materials and Methods:
Eighteen Wistar albino rats exposed to noise for 8 h in a free environment were included. We divided the study population into three groups, and performed daily intraperitoneal injections of papaverine, piracetam, and saline, respectively, throughout the study. We investigated the histopathologic effects of cellular apoptosis on inner hair cells (IHCs) and outer hair cells (OHCs) and compared the distortion product otoacoustic emissions (DPOAEs) thresholds among the groups.
Results and Discussion:
On the 3rd and 7th days, DPOAE thresholds at 8 kHz were significantly higher both in papaverine and piracetam groups compared with the control group ($P = 0.004$ for 3rd day, $P = 0.016$ and $P = 0.028$ for 7th day, respectively). On the 14th day, piracetam group had significantly higher mean thresholds at 8 kHz ($P = 0.029$); however, papaverine group had similar mean thresholds compared to the control group ($P = 0.200$). On the 3rd and 7th days following acoustic trauma, both IHC and OHC loss were significantly lower in both papaverine and piracetam groups. On the 7th day, the mean amount of apoptotic IHCs and OHCs identified using Caspase-3 method were significantly lower in both groups, but the mean amount identified using terminal deoxynucleotidyl transferase dUTP nick end labeling method were similar in both groups compared to the control group.
Conclusion:
We demonstrated the effects of papaverine and piracetam on the recovery of cochlear damage due to acoustic trauma on experimental animals using histopathologic and electrophysiologic examinations.

Otoacoustic emissions versus audiometry in monitoring hearing loss after long-term noise exposure - a systematic review.
Helleman HW, Eising H, Limpens J, Dreschler WA.

Scand J Work Environ Health. 2018 Nov 1;44(6):585-600. doi: 10.5271/sjweh.3725. Epub 2018 Mar 15

Objectives. The objective of this systematic review was to compare otoacoustic emissions (OAE) with audiometry in their effectiveness to monitor effects of long-term noise exposure on hearing. Methods. We conducted a systematic search of MEDLINE, Embase and the non-MEDLINE subset of PubMed up to March 2016 to identify longitudinal studies on effects of noise exposure on hearing as determined by both audiometry and OAE. Results. This review comprised 13 articles, with 30-350 subjects in the longitudinal analysis. A meta-analysis could not be performed because the studies were very heterogeneous in terms of measurement paradigms, follow-up time, age of included subjects, inclusion of data points, outcome parameters and method of analysis. Overall there seemed to be small changes in both audiometry and OAE over time. Individual shifts were detected by both methods but a congruent pattern could not be observed. Some studies found that initial abnormal or low-level emissions might predict future hearing loss but at the cost of low specificity due to a high number of false positives. Other studies could not find such predictive value. Conclusions. The reported heterogeneity in the studies calls for more uniformity in including, reporting and analyzing longitudinal data for audiometry and OAE. For the overall results, both methods showed small changes from baseline towards a deterioration in hearing. OAE could not reliably detect threshold shifts at individual level. With respect to the predictive value of OAE, the evidence was not conclusive and studies were not in agreement. The reported predictors had low specificity.

Prolonged Exposure of CBA/Ca Mice to Moderately Loud Noise Can Cause Cochlear Synaptopathy but Not Tinnitus or Hyperacusis as Assessed With the Acoustic Startle Reflex.

Pienkowski M.

Trends Hear. 2018 Jan-Dec;22:2331216518758109. doi: 10.1177/2331216518758109.

Hearing loss changes the auditory brain, sometimes maladaptively. When deprived of cochlear input, central auditory neurons become more active spontaneously and begin to respond more strongly and synchronously to better preserved sound frequencies. This spontaneous and sound-evoked central hyperactivity has been postulated to trigger tinnitus and hyperacusis, respectively. Localized hyperactivity has also been observed after long-term

exposure to noise levels that do not damage the cochlea. Adult animals exposed to bands of nondamaging noise exhibited suppressed spontaneous and sound-evoked activity in the area of primary auditory cortex (A1) stimulated by the exposure band but had increased spontaneous and evoked activity in neighboring A1 areas. We hypothesized that the cortically suppressed frequencies should for some time after exposure be perceived as less loud than before (hypoacusis), whereas the hyperactivity outside of the exposure band might lead to frequency-specific hyperacusis or tinnitus. To investigate this, adult CBA/Ca mice were exposed for >2 months to 8 to 16 kHz noise at 70 or 75 dB sound pressure level and tested for hypo-/hyperacusis and tinnitus using tone and gap prepulse inhibition of the acoustic startle reflex. Auditory brainstem responses and distortion product otoacoustic emissions showed evidence of cochlear synaptopathy after exposure at 75 but not 70 dB, putting a lower bound on damaging noise levels for CBA/Ca mice. Contrary to hypothesis, neither exposure significantly shifted startle results from baseline. These negative findings nevertheless have implications for startle test methodology and for the putative role of central hyperactivity in hyperacusis and tinnitus.

The impact of biological sex on the response to noise and otoprotective therapies against acoustic injury in mice.

Milon B, Mitra S, Song Y, Margulies Z, Casserly R, Drake V, Mong JA, Depireux DA, Hertzano R.

Biol Sex Differ. 2018 Mar 12;9(1):12. doi: 10.1186/s13293-018-0171-0.

BACKGROUND:

Noise-induced hearing loss (NIHL) is the most prevalent form of acquired hearing loss and affects about 40 million US adults. Among the suggested therapeutics tested in rodents, suberoylanilide hydroxamic acid (SAHA) has been shown to be otoprotective from NIHL; however, these results were limited to male mice.

METHODS:

Here we tested the effect of SAHA on the hearing of 10-week-old B6CBAF1/J mice of both sexes, which were exposed to 2 h of octave-band noise (101 dB SPL centered at 11.3 kHz). Hearing was assessed by measuring auditory brainstem responses (ABR) at 8, 16, 24, and 32 kHz, 1 week before, as well as at 24 h and 15-21 days following exposure (baseline, compound threshold shift (CTS) and permanent threshold shift (PTS), respectively), followed by histologic analyses.

RESULTS:

We found significant differences in the CTS and PTS of the control (vehicle injected) mice to noise, where females had a significantly smaller CTS at 16 and

24 kHz ($p < 0.0001$) and PTS at 16, 24, and 32 kHz (16 and 24 kHz $p < 0.001$, 32 kHz $p < 0.01$). This sexual dimorphic effect could not be explained by a differential loss of sensory cells or synapses but was reflected in the amplitude and amplitude progression of wave I of the ABR, which correlates with outer hair cell (OHC) function. Finally, the frequency of the protective effect of SAHA differed significantly between males (PTS, 24 kHz, $p = 0.002$) and females (PTS, 16 kHz, $p = 0.003$), and the magnitude of the protection was smaller in females than in males. Importantly, the magnitude of the protection by SAHA was smaller than the effect of sex as a biological factor in the vehicle-injected mice.
CONCLUSIONS:
These results indicate that female mice are significantly protected from NIHL in comparison to males and that therapeutics for NIHL may have a different effect in males and females. The data highlight the importance of analyzing NIHL experiments from males and females, separately. Finally, these data also raise the possibility of effectors in the estrogen signaling pathway as novel therapeutics for NIHL.

CDK2 inhibitors as candidate therapeutics for cisplatin- and noise-induced hearing loss.
Teitz T, Fang J, Goktug AN, Bonga JD, Diao S, Hazlitt RA, Iconaru L, Morfouace M, Currier D, Zhou Y, Umans RA, Taylor MR, Cheng C, Min J, Freeman B, Peng J, Roussel MF, Kriwacki R, Guy RK, Chen T, Zuo J.
J Exp Med. 2018 Apr 2;215(4):1187-1203. doi: 10.1084/jem.20172246. Epub 2018 Mar 7.

Hearing loss caused by aging, noise, cisplatin toxicity, or other insults affects 360 million people worldwide, but there are no Food and Drug Administration-approved drugs to prevent or treat it. We screened 4,385 small molecules in a cochlear cell line and identified 10 compounds that protected against cisplatin toxicity in mouse cochlear explants. Among them, kenpaullone, an inhibitor of multiple kinases, including cyclin-dependent kinase 2 (CDK2), protected zebrafish lateral-line neuromasts from cisplatin toxicity and, when delivered locally, protected adult mice and rats against cisplatin- and noise-induced hearing loss. CDK2-deficient mice displayed enhanced resistance to cisplatin toxicity in cochlear explants and to cisplatin- and noise-induced hearing loss in vivo. Mechanistically, we showed that kenpaullone directly inhibits CDK2 kinase activity and reduces cisplatin-induced mitochondrial production of reactive oxygen species, thereby enhancing cell survival. Our experiments have

revealed the proapoptotic function of CDK2 in postmitotic cochlear cells and have identified promising therapeutics for preventing hearing loss.

Assessment of the efficacy of a local steroid rescue treatment administered 2 days after a moderate noise-induced trauma in guinea pig.
Mamelle E, El Kechai N, Adenis V, Nguyen Y, Sterkers O, Agnely F, Bochot A, Edeline JM, Ferrary E.
Acta Otolaryngol. 2018 Jul;138(7):610-616. doi: 10.1080/00016489.2018.1438659. Epub 2018 Mar 5.
OBJECTIVES:
Intratympanic injection of corticosteroids membrane after noise-induced hearing loss is an accepted alternative to general administration. We investigated the effect on hearing of a hyaluronic acid gel with liposomes loaded with dexamethasone (DexP) administered into the middle ear.
METHODS:
An acute acoustic trauma was performed to 13 guinea pigs for a period of 1 h on Day -2. Two 2 days after the noise trauma, the animals were then assigned randomly to four experimental groups: control without gel, gel injection, gel-containing free DexP, gel-containing DexP loaded into liposomes. Auditory thresholds were measured with Auditory Brainstem Response before Day -2 and at Day 0, Day 7 and Day 30 after noise trauma.
RESULTS:
Seven days after, a complete hearing recovery was observed in the control group at all frequencies apart from 8 kHz, and no recovery was observed in the three groups receiving a gel injection. Thirty days after trauma, all of the animals had recovered normal hearing, apart from at the 8-kHz frequency, with similar auditory thresholds.
CONCLUSIONS:
Local DexP administration 48 h after a mild acoustic trauma did not improve hearing recovery, even with a sustained release in a specific gel formulation designed for inner ear therapy.

Direct Reprogramming of Spiral Ganglion Non-neuronal Cells into Neurons: Toward Ameliorating Sensorineural Hearing Loss by Gene Therapy.
Noda T, Meas SJ, Nogami J, Amemiya Y, Uchi R, Ohkawa Y, Nishimura K, Dabdoub A.
Front Cell Dev Biol. 2018 Feb 14;6:16. doi: 10.3389/fcell.2018.00016. eCollection 2018.

Primary auditory neurons (PANs) play a critical role in hearing by transmitting sound information from the inner ear to the brain. Their progressive degeneration is associated with excessive noise, disease and aging. The loss of PANs leads to permanent hearing impairment since they are incapable of regenerating. Spiral ganglion non-neuronal cells (SGNNCs), comprised mainly of glia, are resident within the modiolus and continue to survive after PAN loss. These attributes make SGNNCs an excellent target for replacing damaged PANs through cellular reprogramming. We used the neurogenic pioneer transcription factor Ascl1 and the auditory neuron differentiation factor NeuroD1 to reprogram SGNNCs into induced neurons (iNs). The overexpression of both *Ascl1* and *NeuroD1 in vitro* generated iNs at high efficiency. Transcriptome analyses revealed that iNs displayed a transcriptome profile resembling that of endogenous PANs, including expression of several key markers of neuronal identity: Tubb3, Map2, Prph, Snap25, and Prox1. Pathway analyses indicated that essential pathways in neuronal growth and maturation were activated in cells upon neuronal induction. Furthermore, iNs extended projections toward cochlear hair cells and cochlear nucleus neurons when cultured with each respective tissue. Taken together, our study demonstrates that PAN-like neurons can be generated from endogenous SGNNCs. This work suggests that gene therapy can be a viable strategy to treat sensorineural hearing loss caused by degeneration of PANs.

Bisphosphonate-Linked TrkB Agonist: Cochlea-Targeted Delivery of a Neurotrophic Agent as a Strategy for the Treatment of Hearing Loss.
Kempfle JS, Nguyen K, Hamadani C, Koen N, Edge AS, Kashemirov BA, Jung DH, McKenna CE. Bioconjug Chem. 2018 Apr 18;29(4):1240-1250. doi: 10.1021/acs.bioconjchem.8b00022. Epub 2018 Feb 27.

Hearing loss affects more than two-thirds of the elderly population, and more than 17% of all adults in the U.S. Sensorineural hearing loss related to noise exposure or aging is associated with loss of inner ear sensory hair cells (HCs), cochlear spiral ganglion neurons (SGNs), and ribbon synapses between HCs and SGNs, stimulating intense interest in therapies to regenerate synaptic function. 7,8-Dihydroxyflavone (DHF) is a selective and potent agonist of tropomyosin receptor kinase B (TrkB) and protects the neuron from apoptosis. Despite evidence that TrkB agonists can promote survival of SGNs, local delivery of drugs such as DHF to the inner ear remains a challenge. We previously demonstrated

in an animal model that a fluorescently labeled bisphosphonate, 6-FAM-Zol, administered to the round window membrane penetrated the membrane and diffused throughout the cochlea. Given their affinity for bone mineral, including cochlear bone, bisphosphonates offer an intriguing modality for targeted delivery of neurotrophic agents to the SGNs to promote survival, neurite outgrowth, and, potentially, regeneration of synapses between HCs and SGNs. The design and synthesis of a bisphosphonate conjugate of DHF (Ris-DHF) is presented, with a preliminary evaluation of its neurotrophic activity. Ris-DHF increases neurite outgrowth in vitro, maintains this ability after binding to hydroxyapatite, and regenerates synapses in kainic acid-damaged cochlear organ of Corti explants dissected in vitro with attached SGNs. The results suggest that bisphosphonate-TrkB agonist conjugates have promise as a novel approach to targeted delivery of drugs to treat sensorineural hearing loss.

Persistent hair cell malfunction contributes to hidden hearing loss.
Mulders WHAM, Chin IL, Robertson D.
Hear Res. 2018 Apr;361:45-51. doi: 10.1016/j.heares.2018.02.001. Epub 2018 Feb 14.

Noise exposures that result in fully reversible changes in cochlear neural threshold can cause a reduced neural output at supra-threshold sound intensity. This so-called "hidden hearing loss" has been shown to be associated with selective degeneration of high threshold afferent nerve fiber-inner hair cell (IHC) synapses. However, the electrophysiological function of the IHCs themselves in hidden hearing loss has not been directly investigated. We have made round window (RW) measurements of cochlear action potentials (CAP) and summating potentials (SP) after two levels of a 10 kHz acoustic trauma. The more intense acoustic trauma lead to notch-like permanent threshold changes and both CAP and SP showed reductions in supra-threshold amplitudes at frequencies with altered thresholds as well as from fully recovered regions. However, the interpretation of the results in normal threshold regions was complicated by the likelihood of reduced contributions from adjacent regions with elevated thresholds. The milder trauma showed full recovery of all neural thresholds, but there was a persistent depression of the amplitudes of both CAP and SP in response to supra-threshold sounds. The effect on SP amplitude in particular shows that occult damage to hair cell transduction mechanisms can contribute to hidden hearing loss. Such damage could potentially affect the supra-threshold output properties of surviving primary afferent neurons.

Etiology of Noise-Induced Hearing Loss (NIHL) and its Symptomatic Correlation with Audiometry Observations in Type II Diabetes.
Yadav MK, Yadav KS.
Indian J Otolaryngol Head Neck Surg. 2018 Mar;70(1):137-144. doi: 10.1007/s12070-017-1188-0. Epub 2017 Sep 6.

Type II diabetic mellitus (DM) is a chronic metabolic disease that impairs normal insulin production and glucose transport to the liver and muscles. In the India, about 1-5% population suffer from diabetes or related complication. So there is need to cure this disease. DM chronic auditory complications may include spiral ganglia atrophy, degeneration of the vestibulocochlear nerve myelin sheath, reduction of the number of spiral lamina nerve fibres, and thickening of the capillary walls of the stria vascularis and small arteries. This study aims to know the incidence of common parameters, blood sugar levels, levels of lipids and the hearing thresholds of individuals. It is a Noise-Induced Hearing Loss research study featuring hearing impairment in transport workers diagnosed as type II diabetic. All individuals were interviewed by various questioners related to listening ability of subjects and underwent a physical examination, blood investigations and audiometry. Hearing impairment was more prevalent among adults with diabetes. Sensory neuron hearing loss is predominant in both study groups. Mixed Bilateral Hearing Loss showed significant *p* value in (>.001) by audiometry. The percentage of hearing loss in diabetes (ranges 5.3-28.1%) and in non-diabetics (ranges 3.4-24.1%) and risk factors in diabetes (ranges 22.8-35.1%) over nondiabetics (ranges 17.2-20.1%) which is eye opener. The correlation between type II diabetes and hearing impairment was independent of known risk factors for hearing impairment, such as noise exposure, build-up wax, ototoxic medication, smoking, tobacco chewing etc.

Fluvastatin protects cochleae from damage by high-level noise.
Richter CP, Young H, Richter SV, Smith-Bronstein V, Stock SR, Xiao X, Soriano C, Whitlon DS. Sci Rep. 2018 Feb 14;8(1):3033. doi: 10.1038/s41598-018-21336-7.

Exposure to noise and ototoxic drugs are responsible for much of the debilitating hearing loss experienced by about 350 million people worldwide. Beyond hearing aids and cochlear implants, there have been no other FDA approved drug interventions established in the clinic that would either protect or reverse the effects of hearing loss. Using Auditory Brainstem Responses (ABR) in a guinea pig model, we demonstrate that fluvastatin, an inhibitor of HMG-CoA reductase,

the rate-limiting enzyme of the mevalonate pathway, protects against loss of cochlear function initiated by high intensity noise. A novel synchrotron radiation based X-ray tomographic method that imaged soft tissues at micrometer resolution in unsectioned cochleae, allowed an efficient, qualitative evaluation of the three-dimensional internal structure of the intact organ. For quantitative measures, plastic embedded cochleae were sectioned followed by hair cell counting. Protection in noise-exposed cochleae is associated with retention of inner and outer hair cells. This study demonstrates the potential of HMG-CoA reductase inhibitors, already vetted in human medicine for other purposes, to protect against noise induced hearing loss.

Noise-induced dysregulation of *Quaking* RNA binding proteins contributes to auditory nerve demyelination and hearing loss.
Panganiban CH, Barth JL, Darbelli L, Xing Y, Zhang J, Li H, Noble KV, Liu T, Brown LN, Schulte BA, Richard S, Lang H.
J Neurosci. 2018 Feb 6. pii: 2487-17. doi: 10.1523/JNEUROSCI.2487-17.2018. [Epub ahead of print]

Noise exposure causes auditory nerve (AN) degeneration and hearing deficiency, though the proximal biological consequences are not entirely understood. Most AN fibers and spiral ganglion neurons are ensheathed by myelinating glia that provide insulation and ensure rapid transmission of nerve impulses from the cochlea to the brain. Here we show that noise exposure administered to mice of either sex rapidly affects myelinating glial cells, causing molecular and cellular consequences that precede nerve degeneration. This response is characterized by demyelination, inflammation and widespread expression changes in myelin-related genes, including the RNA splicing regulator *Quaking* (QKI) and numerous QKI target genes. Analysis of mice deficient in QKI revealed that QKI production in cochlear glial cells is essential for proper myelination of spiral ganglion neurons and AN fibers, and for normal hearing. Our findings implicate QKI dysregulation as a critical early component in the noise response, influencing cochlear glia function that leads to AN demyelination and, ultimately, hearing deficiency.

SIGNIFICANCE STATEMENT Auditory glia cells ensheath a majority of spiral ganglion neurons with myelin, protect auditory neurons and allow for fast conduction of electrical impulses along the auditory nerve. Here we show that noise exposure causes glial dysfunction leading to myelin abnormality and

altered expression of numerous genes in the auditory nerve, including QKI, a gene implicated in regulating myelination. Study of a conditional mouse model that specifically depleted QKI in glia showed that QKI deficiency alone was sufficient to elicit myelin-related abnormality and auditory functional declines. These results establish QKI as a key molecular target in the noise response and a causative agent in hearing loss.

The Antioxidant Effect of Rosmarinic Acid by Different Delivery Routes in the Animal Model of Noise-Induced Hearing Loss.

Fetoni AR, Eramo SLM, Di Pino A, Rolesi R, Paciello F, Grassi C, Troiani D, Paludetti G.

Otol Neurotol. 2018 Mar;39(3):378-386. doi: 10.1097/MAO.0000000000001700.

HYPOTHESIS:

Trans-tympanic Rosmarinic Acid (RA), as compared with the systemic administration, protects against noise-induced auditory hair cell and hearing losses in rats in vivo.

BACKGROUND:

ROS production, lipoperoxidative damage, and an imbalance of antioxidant defences play a significant role in noise-induced hearing loss. Several molecules with antioxidant properties have been tested to restore redox homeostasis; however, drug delivery system represents a challenge for their effectiveness. In our model, acute and intense noise exposure induces hearing loss, hair cell death, and oxidative stress, with an increase in superoxide production and over-expression of lipid peroxidation in cochlear structures.

METHODS:

RA was administrated in male Wistar rats by trans-tympanic (20 µl) and systemic (10 mg/kg) modality. In systemic administration, RA was injected 1 hour before noise exposure and once daily for the following 3 days. ABRs were measured before and at days 1, 3, 7, and 30 after noise exposure. Rhodamine-phalloidin staining, dihydroethidium and 8-isoprostane immunostainings were performed to assess and quantify outer hair cells loss, superoxide production, and lipid peroxidation in the different experimental groups.

RESULTS:

Systemic RA administration significantly decreased noise-induced hearing loss and the improvement of auditory function was paralleled by a significant reduction in cochlear oxidative stress. The trans-tympanic modality of drug administration showed a similar degree of protection both at the functional and morphological levels.

CONCLUSION:

The effectiveness of RA given via trans-tympanic injection could be interesting for the future application of this minimally-invasive procedure in the treatment of ROS-induced hearing loss.

Resveratrol Promotes Recovery of Hearing following Intense Noise Exposure by Enhancing Cochlear SIRT1 Activity.
Xiong H, Ou Y, Xu Y, Huang Q, Pang J, Lai L, Zheng Y.
Audiol Neurootol. 2017;22(4-5):303-310. doi: 10.1159/000485312. Epub 2018 Jan 25.

The sirtuin SIRT1 is a highly conserved nicotinamide adenine dinucleotide (NAD)-dependent protein deacetylase known to have protective effects against a wide range of neurological disorders. In the present study, we discovered that C57BL/6 mice fed a long-term diet supplemented with high-dose resveratrol exhibited increased cochlear SIRT1 activity and presented a better recovery of hearing and less loss of hair cells after intense noise exposure compared with those fed a standard chew. Moreover, resveratrol attenuated cochlear SIRT1 decrease and reduced oxidative stress in the cochlea after noise exposure. These results suggest a considerable therapeutic potential of resveratrol for the treatment of noise-induced hearing loss.

Evidence of noise-induced subclinical hearing loss using auditory brainstem responses and objective measures of noise exposure in humans.
Skoe E, Tufts J.
Hear Res. 2018 Apr;361:80-91. doi: 10.1016/j.heares.2018.01.005. Epub 2018 Jan 11.

Exposure to loud sound places the auditory system at considerable risk, especially when the exposure is routine. The current study examined the impact of routine auditory overexposure in young human adults with clinically-normal audiometric thresholds by measuring the auditory brainstem response (ABR), an electrophysiological measure of peripheral and central auditory processing. Sound exposure was measured objectively with body-worn noise dosimeters over a week. Participants were divided into low-exposure and high-exposure groups, with the low-exposure group having an average daily noise exposure dose of ~11% of the recommended exposure limit compared to the high-exposure group average of nearly 500%. Compared to the low-exposure group, the high-exposure group had delayed ABRs to suprathreshold click stimuli and

this prolongation was evident at ABR waves I and III but strongest for V. When peripheral differences were corrected using the I-V interpeak latency, the high-exposure group showed greater taxation at faster stimulus presentation rates than the low-exposure group, suggestive of neural conduction inefficiencies within central auditory structures. Our findings are consistent with the hypothesis that auditory overexposure affects peripheral and central auditory structures even before changes are evident on standard audiometry. We discuss our findings within the context of the larger debate on the mechanisms and manifestations of subclinical hearing loss.

Central and peripheral aspects of noise-induced hearing loss.
Basta D, Gröschel M, Ernst A. HNO.
2018 May;66(5):342-349. doi: 10.1007/s00106-017-0442-9.

Noise is an important socioeconomic problem in industrialized countries. Development of efficient treatment options for the audiological phenomena resulting from noise-induced hearing loss requires in-depth understanding of the underlying damage mechanisms causing peripheral and central nervous changes. Mechanical damage, ischemia and excitotoxicity are mainly responsible for noise-induced cell death and biophysical changes in the cochlea. Auditory synaptopathy is an additional consequence. Besides these cochlear pathologies, noise exposure leads to extensive changes within the central auditory pathway. Overstimulation causes early cell loss in the ventral cochlear nucleus just after noise exposure, which is in accordance with enhancement of apoptotic mechanisms within the corresponding timeframe. In contrast to the cell loss in lower auditory structures due to overstimulation, the later significant reduction of cell density in higher auditory structures is due to sensory deprivation. Changes in network homeostasis seem to partially compensate structural losses by modulation of spontaneous activity. However, central nervous processing of auditory information is permanently impaired by the neuroplastic changes. Unfortunately, the various noise-induced peripheral and central pathologies are difficult to treat. New therapeutic approaches are required, particularly for treatment of central nervous processing disorders and auditory synaptopathy, which contribute to audiological phenomena such as tinnitus, hyperacusis and poor speech perception in noise.

Effects of intratympanic dexamethasone on noise-induced hearing loss: An experimental study.

Gumrukcu SS, Topaloglu İ, Salturk Z, Tutar B, Atar Y, Berkiten G, Göker AE. Am J Otolaryngol. 2018 Jan - Feb;39(1):71-73. doi: 10.1016/j.amjoto.2017.10.011. Epub 2017 Oct 27.

AIM:
Aim of the study was to evaluate the effect of intratympanic steroid treatment on hearing based on oto-acoustic emission.
METHODS:
A total of 16 healthy female Wistar albino rats weighing were used in this study. They were divided in to 2 groups and each group was exposed to noise at 110dB for 25min to induce acoustic trauma. Intratympanic dexamethasone was administered to the middle ears of animals in the experimental group on the same day as exposure to noise. The control group was given 0.09% saline solution. Distortion product otoacoustic emission measurements were performed on days 7 and 10.
RESULTS:
There were no differences between the emission results of two groups before treatment at 4004, 4761, 5652, 6726, and 7996Hz. There were significant group differences on measurement days 7 and 10 at all frequencies.
CONCLUSION:
Our study revealed a significant difference in DPOAE measurements on days 7 and 10 between the experimental and control groups. We detected a positive effect of dexamethasone on noise-induced hearing loss.

Effect of antioxidant supplementation on the auditory threshold in sensorineural hearing loss: a meta-analysis.

Souza MEDCA, Costa KVTD, Vitorino PA, Bueno NB, Menezes PL.
Braz J Otorhinolaryngol. 2018 May - Jun;84(3):368-380. doi: 10.1016/j.bjorl.2017.07.011. Epub 2017 Aug 26.

INTRODUCTION:
Hearing loss is conceptualized as any impairment of the ability to hear and/or detect speech or environment sounds, regardless of cause, type, or degree. It may occur at different stages of life; during pregnancy or childbirth, in childhood, adulthood or old age. It should be noted that aging is the most common cause of sensorineural hearing loss followed by noise-induced hearing loss, and both are closely related to the formation of reactive oxygen species.

Dietary antioxidant supplementation has been employed as a therapeutic strategy to prevent and/or delay the risks of major human diseases.
OBJECTIVE:
To assess randomized clinical trials to determine the effect of antioxidant supplementation on the auditory thresholds in patients of different age groups with sensorineural hearing loss.
METHODS:
This systematic review consisted of a search in the following databases: MEDLINE, CENTRAL, ScienceDirect, Scopus, Web of Science, LILACS, SciELO and ClinicalTrials.gov. Additionally, the gray literature was also searched. The search strategy included terms related to the intervention (antioxidant supplementation), primary outcome (sensorineural hearing loss), as well as terms related to randomized clinical trials to improve search sensitivity.
RESULTS:
Based on 977 potentially relevant records identified through the search in the databases, ten full-text publications were retrieved for further evaluation. The increase in threshold at the 4kHz frequency was statistically higher in the control group (1.89 [1.01-2.78], p<0.0001) when compared to the NAC group and the ginseng group, whereas at 6kHz, the threshold increase was higher in the control group (1.42 [-1.14-3.97], p=0.28), but no statistically significant differences were found between groups.
CONCLUSION:
Ginseng was the antioxidant agent that showed the best effect in preventing auditory threshold worsening at the frequency of 4kHz, but not at 6kHz in patients with sensorineural hearing loss caused by exposure to high sound pressure levels. There was no improvement in the thresholds with vitamin E supplementation.

Prevention of cisplatin-induced hearing loss in children: Informing the design of future clinical trials.
Minasian LM, Frazier AL, Sung L, O'Mara A, Kelaghan J, Chang KW, Krailo M, Pollock BH, Reaman G, Freyer DR.
Cancer Med. 2018 May 30. doi: 10.1002/cam4.1563. [Epub ahead of print]

Cisplatin is an essential chemotherapeutic agent in the treatment of many pediatric cancers. Unfortunately, cisplatin-induced hearing loss (CIHL) is a common, clinically significant side effect with life-long ramifications, particularly for young children. ACCL05C1 and ACCL0431 are two recently completed

Children's Oncology Group studies focused on the measurement and prevention of CIHL. The purpose of this paper was to gain insights from ACCL05C1 and ACCL0431, the first published cooperative group studies dedicated solely to CIHL, to inform the design of future pediatric otoprotection trials. Use of otoprotective agents is an attractive strategy for preventing CIHL, but their successful development must overcome a unique constellation of methodological challenges related to translating preclinical research into clinical trials that are feasible, evaluate practical interventions, and limit risk. Issues particularly important for children include use of appropriate methods for hearing assessment and CIHL severity grading, and use of trial designs that are well-informed by preclinical models and suitable for relatively small sample sizes. Increasing interest has made available new funding opportunities for expanding this urgently needed research.

An Oral Combination of Vitamins A, C, E, and Mg^{++} Improves Auditory Thresholds in Age-Related Hearing Loss.
Alvarado JC, Fuentes-Santamaría V, Gabaldón-Ull MC, Juiz JM.
Front Neurosci. 2018 Jul 31;12:527. doi: 10.3389/fnins.2018.00527. eCollection 2018.

The increasing rate of age-related hearing loss (ARHL), with its subsequent reduction in quality of life and increase in health care costs, requires new therapeutic strategies to reduce and delay its impact. The goal of this study was to determine if ARHL could be reduced in a rat model by administering a combination of antioxidant vitamins A, C, and E acting as free radical scavengers along with Mg^{++}, a known powerful cochlear vasodilator (ACEMg). Toward this goal, young adult, 3 month-old Wistar rats were divided into two groups: one was fed with a diet composed of regular chow ("normal diet," ND); the other received a diet based on chow enriched in ACEMg ("enhanced diet," ED). The ED feeding began 10 days before the noise stimulation. Auditory brainstem recordings (ABR) were performed at 0.5, 1, 2, 4, 8, 16, and 32 kHz at 3, 6-8, and 12-14 months of age. No differences were observed at 3 months of age, in both ND and ED animals. At 6-8 and 12-14 months of age there were significant increases in auditory thresholds and a reduction in the wave amplitudes at all frequencies tested, compatible with progressive development of ARHL. However, at 6-8 months threshold shifts in ED rats were significantly lower in low and medium frequencies, and wave amplitudes were significantly larger at all frequencies when compared to ND rats. In the oldest animals,

differences in the threshold shift persisted, as well as in the amplitude of the wave II, suggesting a protective effect of ACEMg on auditory function during aging. These findings indicate that oral ACEMg may provide an effective adjuvant therapeutic intervention for the treatment of ARHL, delaying the progression of hearing impairment associated with age.

Effectiveness of Auditory Measures for Detecting Hidden Hearing Loss and/or Cochlear Synaptopathy: A Systematic Review.
Barbee CM, James JA, Park JH, Smith EM, Johnson CE, Clifton S, Danhauer JL. Semin Hear. 2018 May;39(2):172-209. doi: 10.1055/s-0038-1641743. Epub 2018 Jun 15.

Standard audiometric evaluations are not sensitive enough to identify hidden hearing loss (HHL) and/or cochlear synaptopathy (CS). Patients with either of these conditions frequently present with difficulty understanding speech in noise or other complaints such as tinnitus. The purpose of this systematic review is to identify articles in peer-reviewed journals that assessed the sensitivity of audiologic measures for detecting HHL and/or CS, and which showed potential for use in a clinical test battery for these disorders. A reference librarian submitted specific boolean terminology to MEDLINE, Embase, and Web of Science. The authors used a consensus approach with specially designed score sheets for the selection of titles, abstracts, and then articles for inclusion in the systematic review and for quality assessment. Fifteen articles were included in the systematic review. Seven articles involved humans; seven involved animals, and one study used both humans and animals. Results showed that pure-tone audiometry to 20 kHz, otoacoustic emissions, electrocochleography, auditory brainstem response (ABR), electrophysiological tests, speech recognition in noise with and without temporal distortion, interviews, and self-report measures have been used to assess HHL and/or CS. For HHL, ultra-high-frequency audiometry may help identify persons with sensory hair cell loss that does not show up on standard audiograms. Promising nonbehavioral measures for CS included ABR wave I amplitude, the summating potential-to-action potential ratio, and speech recognition in noise with and without temporal distortion. Self-report questionnaires also may help identify auditory dysfunction in persons with normal hearing

Animal model studies yield translational solutions for cochlear drug delivery.

Frisina RD, Budzevich M, Zhu X, Martinez GV, Walton JP, Borkholder DA.
Hear Res. 2018 Oct;368:67-74. doi: 10.1016/j.heares.2018.05.002. Epub 2018 May 5.

The field of hearing and deafness research is about to enter an era where new cochlear drug delivery methodologies will become more innovative and plentiful. The present report provides a representative review of previous studies where efficacious results have been obtained with animal models, primarily rodents, for protection against acute hearing loss such as acoustic trauma due to noise overexposure, antibiotic use and cancer chemotherapies. These approaches were initiated using systemic injections or oral administrations of otoprotectants. Now, exciting new options for local drug delivery, which opens up the possibilities for utilization of novel otoprotective drugs or compounds that might not be suitable for systemic use, or might interfere with the efficacious actions of chemotherapeutic agents or antibiotics, are being developed. These include interesting use of nanoparticles (with or without magnetic field supplementation), hydrogels, cochlear micropumps, and new transtympanic injectable compounds, sometimes in combination with cochlear implants.

Environmental exposure of heavy metal (lead and cadmium) and hearing loss: data from the Korea National Health and Nutrition Examination Survey (KNHANES 2010-2013).
Kang GH[1], Uhm JY[1], Choi YG[1], Kang EK[1], Kim SY[1], Choo WO[1], Chang SS[1].
Ann Occup Environ Med. 2018 Apr 17;30:22. doi: 10.1186/s40557-018-0237-9. eCollection 2018.
Background:
Lead and cadmium have been identified as risk factors for hearing loss in animal studies, but large-scale studies targeting the general human population are rare. This study was conducted to investigate the link between heavy metal concentrations in blood and hearing impairment, using a national population-based survey.
Methods:
The study participants comprised 6409 Koreans aged 20 or older, who were included in the Fifth and Sixth Korea National Health and Nutrition Examination Surveys (KNHANES 2010-2013). Hearing impairment was categorized into two types, low- and high-frequency hearing impairment, using pure tone audiometry. Low-frequency hearing impairment was defined as having a binaural average of hearing thresholds for 0.5, 1, and 2 kHz exceeding 25 dB,

and high-frequency hearing impairment was defined as having a binaural average of hearing thresholds for 3, 4, and 6 kHz exceeding 25 dB. The blood levels of heavy metals (lead and cadmium) were classified into quartiles. Cross-sectional association between hearing impairment and the level of heavy metals (lead and cadmium) was examined in both sexes. Multivariate logistic regression was used to obtain adjusted odds ratios (ORs) and 95% confidence intervals (CIs).
Results:
Among men, the prevalence of low- and high- frequency hearing impairment was 13.9% and 46.7%, respectively, which was higher than the prevalence among women (11.8% and 27.0%, respectively). Regarding lead, the adjusted OR of high-frequency hearing impairment for the highest blood level group versus the lowest group was significant in both men (OR = 1.629, 95% CI = 1.161-2.287) and women (OR = 1.502, 95% CI = 1.027-2.196), after adjusting for age, body mass index, education, smoking, alcohol consumption, exercise, diagnosis of diabetes mellitus, hypertension, and noise exposure (occupational, loud, firearm noises). No links were found between blood lead levels and low-frequency hearing impairment, or between blood cadmium levels and low- or high-frequency hearing impairment in either sex.
Conclusions:
The present study findings suggest that even exposure to low-level lead is a risk factor for high-frequency hearing loss. A prospective epidemiologic study should be conducted to identify the causal relationship between human health and exposure to heavy metals, and efforts to reduce heavy metal exposure in the general population should continue.

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CLINICAL TRIALS

ClinicalTrials.gov was searched using the following search terms: "noise induced hearing loss," "hearing loss" AND "noise", and "noise-induced tinnitus". "Include

only open studies" was selected and the search results, retrieved September 2018, derived 2, 74, and 1 result, respectively, for a total of 77 results. 2 duplicates were removed leaving 75 studies for review. Studies were further eliminated from inclusion based on subjective determination of relevance by the editors for a total of 33 studies included below.

It should be noted that relevance was considered broadly as any studies of potential interest, including in secondary outcomes listed, to any one of the PIHL committee focus areas (see editor's introduction for the general listing of these). An exception to the PIHL focus areas used was the category of noise exposure, to include both measurement and preventative assessments, as this opens such a large category of studies, not all of which would necessarily categorize as a clinical trial nor be required to register in clinicaltrials.gov, and thus inclusion herein would produce an indeterminately incomplete set. In studies where primary or secondary outcomes assessed an intervention for hearing or tinnitus outcomes the studies were included, whereas studies which only captured hearing or tinnitus outcomes as adverse events were excluded. This most predominantly occurred in ototoxicity studies.

TITLE: Prevention of Noise-induced Damage by Use of Antioxidants
CT.gov ID: NCT01727492
Responsible Party: University Hospital, Antwerp
Target Condition(s): Noise-induced Tinnitus, Noise-induced Hearing Loss
Intervention: Drug: Antioxidantia
Phase: Not applicable
Study Start Date: November 2012
Description Provided: The current study is a dubble-blinde placebo-controlled cross-over study verifying the preventive effect of antioxidants on noise-induced hearing loss (NIHL) and noise-induced tinnitus (NIT). The antioxidants comprise of a mixture of magnesium and n-acetylcystein which should be taken 1h before leisure noise above 100dB for at least 30 minutes.
URL:
https://clinicaltrials.gov/ct2/show/NCT01727492?term=NCT01727492&rank=1

TITLE: Blast Exposed Veterans With Auditory Complaints
CT.gov ID: NCT02122458
Responsible Party: VA Office of Research and Development
Target Condition(s): Hearing impairment, hearing aid fitting
Intervention: Device: mild-gain hearing aids

Phase: 1
Study Start Date: August 1, 2015
Description Provided: The purpose of this study is to study blast-exposed Veterans who report hearing handicap but show normal or near normal results on standard audiometric testing. The characteristics and nature of their auditory and auditory-related skills will be examined, along with whether coexisting PTSD contributes to the hearing problems of these Veterans. In a preliminary treatment study, a sub-sample of these Veterans will be fitted with mild-gain hearing aids to determine if they benefit from low-level amplification of high-frequency sounds.
URL:
https://clinicaltrials.gov/ct2/show/NCT02122458?term=NCT02122458&rank=1

TITLE: Risk Factors for Hearing Loss as a Result of Exposure to Noise During Military Training in the IDF
CT.gov ID: NCT03314116
Responsible Party: Medical Corps, Israel Defense Force
Target Condition(s): Noise- induced hearing loss
Intervention: Guidance on auditory protection
Phase: Not applicable
Study Start Date: August 1, 2017
Description Provided: As part of the proposed work, the investigators would like to examine whether there is a need to use a training video to train IDF combat soldiers to improve the use of ear plugs and to prevent hearing loss from exposure to noise, and to characterize the hearing impaired epidemiology of recruits and the basic rate of hearing loss During basic training.
URL:
https://clinicaltrials.gov/ct2/show/NCT03314116?term=NCT03314116&rank=1

TITLE: The Effects of Ultrasonic Noise Exposure on Human Hearing
CT.gov ID: NCT03515928
Responsible Party: Ultrahaptics Ltd
Target Condition(s): Hearing Loss
Intervention: Ultrasonic noise exposure, Diagnostic Test: Pure Tone Audiometry
Phase: Not Applicable
Study Start Date: May 2018
Description Provided: The aim of this research is to investigate the effects of ultrasonic noise exposure on the human auditory system (how it effects hearing). Current international regulations concerning ultrasound exposure differs

significantly and are based on scarce and outdated scientific data; hence the motivation for this research. A cohort of 20 audiometrically healthy volunteers will undergo pure tone audiometry (PTA); a standard test for hearing sensitivity, at both pre and post exposure to ultrasonic noise (40kHz for 15 min at 120 dB SPL). A subgroup of 10 subjects will be used as a control group. The resulting audiograms will establish the extent of any recoverable loss in hearing sensitivity known as temporary threshold shifts (TTS).
URL:
https://clinicaltrials.gov/ct2/show/NCT03515928?term=NCT03515928&rank=1

TITLE: A Phase 2b Study of SPI-1005 to Prevent Acute Noise Induced Hearing Loss (PANIHL)
CT.gov ID: NCT02779192
Responsible Party: Sound Pharmaceuticals, Incorporated
Target Condition(s): Acute noise- induced hearing loss
Intervention: Drug: SPI-1005 200mg, Drug: SPI-1005 400mg, Drug: Placebo
Phase: 2b
Study Start Date: November 2018
Description Provided: SPI-1005 is a novel oral drug that contains a glutathione peroxidase mimetic (ebselen) that will be tested in subjects with a history of NIHL at risk for additional NIHL. The goal of this multi-center Phase 2b study is to determine whether SPI-1005 is effective in reducing an acute NIHL in this affected population. In this Phase 2b study subjects with prior NIHL will be enrolled and exposed to a calibrated sound challenge (CSC) that induces a slight acute NIHL.
URL:
https://clinicaltrials.gov/ct2/show/NCT02779192?term=NCT02779192&rank=1

TITLE: Localization and Mismatch Negativity (MMNLocA)
CT.gov ID: NCT03632551
Responsible Party: University Hospital, Toulouse
Target Condition(s): Deafness
Intervention: Other: Specific binaural hearing evaluations
Phase: Not applicable
Study Start Date: September 2018

Description Provided: This descriptive and observational research project aims to characterize MMN as a neuronal marker of localization deficit in single-sided deafened subjects and subjects with bilateral profound deafness treated by a

cochlear implant (CI). It includes several electro-physiological and psychoacoustic assessments performed on subjects with single-sided deafness and cochlear implanted subjects, with normal-hearing subjects as control:

Evaluation of the characteristics of the MMN involved in sound localization by EEG, evaluation of the spatial localization abilities for a sound source presented in the open field, assessment of performance for speech recognition in noise. These evaluations are performed in subjects with symmetrical hearing, in a natural binaural condition and a monaural condition (with a plugged ear), in subjects with single-sided deafness and in subjects with unilateral CI.

URL:
https://clinicaltrials.gov/ct2/show/NCT03632551?term=NCT03632551&rank=1

TITLE: Effects of Short-term Choir Participation on Auditory Perception in Hearing-aided Older Adults.
CT.gov ID: NCT03604185
Responsible Party: Ryerson University
Target Condition(s): Hearing LossAuditory PerceptionMusic TherapyAging
Intervention: Behavioral: Choir Singing, Behavioral: Music Appreciation
Phase: Not applicable
Study Start Date: September 1, 2018
Description Provided: Hearing loss has been associated with decreased emotional wellbeing and reduced quality of life in aging adults. Although hearing aids can target aspects of peripheral hearing loss, persistent perceptual deficits are widely reported. One prevalent example is the loss of the ability to perceive speech in a noisy environment, which severely impacts quality of life and goes relatively unremediated by hearing aids. Musicianship has been shown to improve aspects of auditory processing, but has not been studied as a short-term intervention for improving these abilities in older adults with hearing aids. The current study investigates whether short-term choir participation can improve three aspects of auditory processing: perception of speech in noise, pitch discrimination, and the neural response to brief auditory stimuli (frequency following response; FFR). Sixty hearing aided older adults (aged 50+) recruited from the Greater Toronto Area will be randomly assigned to one of three conditions: a choir singing class (n=20), a music appreciation class (n=20), and a do-nothing control group (n=20). Choir participants will take part in a singing class for 14 weeks, during which they will take part in group singing (2 hours/week) supported by individual online musical training (1 hour/week).

Participants will undergo pre- and post-training assessments, conducted during the first week of the choir class and again after the last week. Participants in the music appreciation class will be involved in 14 weeks of music listening classes, and the do-nothing control group will not engaged in an active intervention. All participants will undergo the same battery of assessments, measured before and after the 14-week time frame. Auditory assessments (speech perception in noise and pitch discrimination tests) will be administered electronically, and the FFR will be obtained using electroencephalography (EEG). Each of the four assessment sessions (two pre-training, two post-training) will last approximately 1.5 hours, for a total of 6 hours of data collection. The goal of this research is to investigate whether short-term musical training will result in improved auditory outcomes for older adults with hearing aids. It is predicted that the choir singing group will demonstrate the greatest improvements across all auditory measures, and that both the choir singing and musical appreciation groups will experience greater improvements than the do-nothing control group.
URL:
https://clinicaltrials.gov/ct2/show/NCT03604185?term=NCT03604185&rank=1

TITLE: Study of Binaural Squelch Effect in Unilateral Otosclerosis (CBOU)
CT.gov ID: NCT03587792
Responsible Party: University Hospital, Grenoble
Target Condition(s): Otosclerosis of Middle Ear, Unilateral Hearing Loss
Intervention: Procedure: stapedectomy
Phase: Not specified
Study Start Date: March 6, 2018
Description Provided: Patients with unilateral transmissional hypoacousis due to otosclerosis undergoing stapedectomy surgery will be prospectively included. They will be undergoing a free field vocal audiometry using the Oldenburg MATRIX software to evaluate the squelch effect gain between audiometry before and after 9months after surgery. Our hypothesis is to show a squelch effect with the rehabilitation of the binaural audition.

URL:
https://clinicaltrials.gov/ct2/show/NCT03587792?term=NCT03587792&rank=1

TITLE: Validation of a Smartphone-Based Hearing-in-Noise Test (HearMe) (HearMe)
CT.gov ID: NCT03429777
Responsible Party: Kasra Zarei

Target Condition(s): Hearing Loss, Hearing Disorders, Hearing Abnormality, Hearing Disability, Tinnitus
Intervention: Device: HearMe Smartphone Application
Phase: 2
Study Start Date: August 1, 2019
Description Provided: The purpose of this project is to validate a quick, easy-to-use and administer smartphone hearing-in-noise test. The Hearing-in-Noise Test (HINT) measures an individual's ability to hear speech in quiet and in noise. HINTs are traditionally done testing both ears together as binaural hearing ability is key in noisy settings and everyday, functional hearing.
The app (called HearMe) can potentially be used to easily and quickly collect hearing-in-noise and speech-in-noise measurements. The smartphone app developed is a hearing-in-noise test that presents the subject with a series of stimuli consisting of a spoken three-digit sequence presented at a varying hearing-to-noise ratio. For each stimulus presentation, the user tap the three-digit sequence. The duration of the app is less than 3 minutes. For this project the investigators will test at least 50 subjects with hearing loss and 50 control subjects between the ages of 18-80. The subjects will be invited to take the app. The approach for this pilot study is to characterize hearing-in-noise thresholds (also referred to as a speech-reception threshold) as measured by the app in both subject groups, and relate it to the phenotype of each group as a preliminary evaluation of the app as well as a preliminary validation against their routinely collected measurements of hearing function (pure-tone audiometry thresholds).

The study will assess the validity of the test construct in measuring hearing-in-noise thresholds, and serve as a foundation for further iterative designs of the app and future validation and characterization studies. This study seeks to validate a developed smartphone HINT on an initial cohort of patients and controls. It is anticipated that patients with hearing loss will display higher signal-to-noise ratio thresholds (as measured by the iPhone app) compared to controls.
URL:
https://clinicaltrials.gov/ct2/show/NCT03429777?term=NCT03429777&rank=1

TITLE: Treating Hearing Loss to Improve Mood and Cognition in Older Adults
CT.gov ID: NCT03321006
Responsible Party: New York State Psychiatric Institute
Target Condition(s): Hearing Loss, Depression
Intervention: Device: Audio B-R 90 hearing aid device, Drug: Duloxetine

Phase: 4
Study Start Date: August 15, 2017
Description Provided: Age-related hearing loss (ARHL) is the third most common health condition affecting older adults after heart disease and arthritis and is the fifth leading cause of years lived with disability worldwide. Many hearing-impaired older adults avoid or withdraw from social contexts in which background noise will make it difficult to communicate, resulting in social isolation and reduced communication with family and friends.Social isolation and loneliness have been linked to numerous adverse physical and mental health outcomes, including dementia, depression, and mortality, and they may also lead to declining physical activity and the development of the syndrome of frailty. In this project it is hypothesized that untreated ARHL represents a distinct route to developing Late-life Depression (LLD) and that individuals with comorbid ARHL/LLD are unlikely to respond to treatments (i.e., antidepressant medication) that do not treat the underlying hearing problem. Initial studies suggest remediation of hearing loss using hearing aids or cochlear implantation may decrease depressive symptoms acutely and over the course of 6 to 12 months follow-up. However, the clinical significance of these findings is obscured by lack of rigorous control groups, failure to objectively document hearing aid compliance, and enrollment of study populations lacking syndromal depression or even a threshold symptom score.
URL:
https://clinicaltrials.gov/ct2/show/NCT03321006?term=NCT03321006&rank=1

TITLE: Big Data Supporting Public Health Hearing Policies (EVOTION)
CT.gov ID: NCT03316287
Responsible Party: University College, London
Target Condition(s): hearing loss
Intervention: Device: Hearing aid, Device: Mobile phone, Device: Sensor
Phase: not applicable
Study Start Date: March 1, 2018
Description Provided: Hearing Loss (HL) affects over 5% of the world's population (WHO 2014) and is the 5th leading cause of Years Lived with Disability. HL is currently managed with Hearing Aids (HAs), i.e. programmable sound amplification devices that are worn by the hearing impaired subjects to address their hearing difficulties. HA use however is often problematic, costly and with poor overall benefits. The holistic management of HL requires appropriate public health policies for HL prevention, early diagnosis, long-term treatment and rehabilitation; detection and prevention of cognitive decline; and

socioeconomic inclusion of HL patients. Currently the evidential basis for forming such policies is limited.
The EVOTION project proposes to address this by collecting and analysing a big set of heterogeneous data, including HA usage, audiological, physiological, cognitive, clinical and medication, personal, behavioural, life style, occupational and environmental data.

This will be done by:

i. accessing big datasets of existing HA user data from the EVOTION clinical partners (UCL/UCLH and GST in the UK; OTICON in Denmark) ii. collection of prospective HA user data who will be recruited to the prospective EVOTION study and who will undergo some additional assessments iii. collection of real time dynamic data of the human participant HA users who will be given a smart phone with different apps (auditory tests; auditory training), sensors (recording of heart rate, blood pressure, respiratory rate etc.) and smart HAs (recording environmental factors such as noise levels, type of noise etc.) so that real life contextual factors that affect HA usage and outcome can be identified.

These data will be analysed with big data analysis/data mining techniques in order to identify relationships between these in order to use this information to derive and support public health decisions.
URL:
https://clinicaltrials.gov/ct2/show/NCT03316287?term=NCT03316287&rank=1

TITLE: Hearing Loss and the Effects of Statin Drugs in People With Head and Neck Squamous Cell Carcinoma Treated With Cisplatin Chemoradiation
CT.gov ID: NCT03225157
Responsible Party: National Institute on Deafness and Other Communication Disorders (NIDCD)
Target Condition(s): Head and Neck Cancer, Hearing Disorder, Hyperlipidemia
Intervention: Not specified
Phase: Not specified
Study Start Date: September 13, 2018
Description Provided: Cisplatin is a chemotherapy drug. It is used to treat head and neck squamous cell carcinoma (HNSCC) and other cancers. It can cause hearing loss for some people. It is not known how many people will get hearing loss from cisplatin. It is also not known what other factors might influence who gets hearing loss. Factors could include age, sex, noise exposure, and other drugs the person is taking. Statins are drugs used to lower cholesterol. Statins may also reduce cisplatin-induced hearing loss.

Objectives: To see if statins reduce hearing loss in people getting cisplatin therapy to treat HNSCC. To find out how many people taking cisplatin get hearing loss from it. To find out if other factors might influence whether cisplatin causes hearing loss.

Eligibility: People ages 18 and older who are getting treatment with cisplatin for HNSCC

Design: Participants will be screened with a review of their medical records.

Participants will have 3 visits. These will be before the onset of cisplatin therapy, at about 4 weeks after they finish therapy, and about 6 months after they finish therapy. Each visit will include: Medication history

Audiogram/hearing tests. Participants will wear headphones and indicate when they hear different sounds. Questions about their noise exposure history and whether they have ringing in the ears.

URL:
https://clinicaltrials.gov/ct2/show/NCT03225157?term=NCT03225157&rank=1

TITLE: The RBANS-H in Older Adults With Normal Hearing or Age-related Hearing Loss (RBANS-H_ARHL)
CT.gov ID: NCT03208608
Responsible Party: University Hospital, Antwerp
Target Condition(s): Normal hearing
Intervention: Diagnostic Test: RBANS-H
Phase: Not specified
Study Start Date: November 21, 2016
Description Provided: The present cross-sectional study aims to examine the cognitive capabilities of older adults, aged 50 to 89, with normal hearing or age-related hearing loss by means of the Repeatable Battery for the Assessment of Neuropsychological Status for Hearing impaired individuals (RBANS-H). Secondly, the correlations between cognition on the one hand and hearing and speech reception capabilities on the other hand are investigated. For this purpose, twenty participants are included in the age categories 50 to 59, 60 to 69, 70 to 79 and 80 to 89, bringing the total number to 80. Three questionnaires are administered to the participants: the Health Utilities Index-2/3 (HUI 2/3), Dizziness Handicap Inventory (DHI) and a general questionnaire on education and profession, medical history, hearing aid use and tinnitus. Also an audiological

examination is performed, including pure tone audiometry, speech in quiet and speech in noise audiometry. Finally, cognition is assessed using the RBANS-H.
URL:
https://clinicaltrials.gov/ct2/show/NCT03208608?term=NCT03208608&rank=1

TITLE: Positron Emission Tomography Imaging of Brain Reorganisation of the Central Auditory Cortex in Asymetrical Profound Deaf Patient With a Cochlear Implantation. (UniTEP)
CT.gov ID: NCT03117413
Responsible Party: University Hospital, Toulouse
Target Condition(s): Profound hearing impairment
Intervention: Other: Positron emission tomography scanvv
Phase: Not applicable
Study Start Date: May 2017
Description Provided: Our main objective is to study how the extent of reorganization of the central auditory system is related to the binaural integration in cochlear implanted subjects with asymmetric hearing loss. Subjects with asymmetric hearing loss treated with a cochlear implant and a control group of normal hearing subjects will perform two tests for binaural integration (speech recognition in noise and spatial localization) and two tasks of non-linguistic sounds perception.
URL:
https://clinicaltrials.gov/ct2/show/NCT03117413?term=NCT03117413&rank=1

TITLE: Auditory Nerve Monitoring Using Intra-cochlear Stimulation in Subjects With Acoustic Neuroma (NeuriStim)
CT.gov ID: NCT02948790
Responsible Party: Oticon Medical
Target Condition(s): Hearing Loss, Cochlear, Neurinoma of the Acoustic Nerve
Intervention: Device: NeuristimDevice: Cochlear implant
Phase: Not applicable
Study Start Date: March 2017
Description Provided: The aim of this study is to assess the auditory nerve functionality with an intraoperative approach following a surgical removal of acoustic neuroma in patients with severe to profound sensorineural hearing disabilities.
URL:
https://clinicaltrials.gov/ct2/show/NCT02948790?term=NCT02948790&rank=1

TITLE: Benefits of the HiResolution Bionic Ear System in Adults With Asymmetric Hearing Loss
CT.gov ID: NCT02811549
Responsible Party: Advanced Bionics
Target Condition(s): Hearing Loss, Ear Diseases, Hearing Disorders, Otorhinolaryngologic Diseases, Asymmetrical Hearing Loss, Single-Sided Deafness
Intervention: Device: HiResolution Bionic Cochlear Implant
Phase: Not applicable
Study Start Date: November 28, 2016
Description Provided: The purpose of this feasibility study is to evaluate the benefit of unilateral implantation in adults who have severe to profound sensorineural hearing loss in one ear, and up to moderate sensorineural hearing loss in the other ear (asymmetric hearing loss).
URL:
https://clinicaltrials.gov/ct2/show/NCT02811549?term=NCT02811549&rank=1

TITLE: Tinnitus Suppression for Cochlear Implant Recipients
CT.gov ID: NCT02794623
Responsible Party: The Hearing Cooperative Research Centre
Target Condition(s): Tinnitus
Intervention: Device: Tinnitus masking
Phase: Not applicable
Study Start Date: October 2014
Description Provided: Tinnitus is the perception of sound in the absence of an external sound. Prevalence in the general population is 10 to 15%, with tinnitus severely impacting quality of life in 1-2 percent of the population. Tinnitus therapy is based on counselling, cognitive and behavioural therapies in combination with sound therapies which mostly rely on masking.
For cochlear implant candidates, the ability to use hearing aids and maskers is limited by the degree of their hearing loss. Reports of tinnitus prevalence in this group range from 67 to 100% with a mean of 80%.

In cochlear implant (CI) recipients, tinnitus suppression primarily occurs during active use of the cochlear implant system. In some CI recipients residual inhibition of tinnitus occurs when the implant is switched off. While the benefits of CI implantation on tinnitus are well documented, there is a group of recipients where tinnitus remains a concern in the implanted ear post-operatively.

The primary aim of this study is to investigate the benefits of using tinnitus masking via a CI sound processor that optimises tinnitus suppression with minimal annoyance to the user. Furthermore a questionnaire will be employed to capture the prevalence, degree and nature of tinnitus in recipients.
URL:
https://clinicaltrials.gov/ct2/show/NCT02794623?term=NCT02794623&rank=1

TITLE: RBANS-H in Older Patients Before and After Cochlear Implantation: A Protocol for a Prospective Study (RBANS-H-CI-A)
CT.gov ID: NCT02794350
Responsible Party: University Hospital, Antwerp
Target Condition(s): hearing impaired
Intervention: Device: Cochlear implant
Phase: Not specified
Study Start Date: July 2015
Description Provided: The cognitive profile of older adults with a severe to profound hearing impairment is determined by means of the Repeatable Battery for the Assessment of Neuropsychological Status, adjusted for Hearing impaired subjects (RBANS-H) before and after cochlear implantation. In this prospective, longitudinal study the participants are tested preoperatively, at six months and twelve months postoperatively and from then on yearly up to 10 years after implantation. In addition to the RBANS-H an audiological examination and an semistructured interview is conducted concerning the cochlear implant use and the self-reliance of the patient and subjective questionnaires are filled out by the subjects to assess quality of life and hearing benefit.
URL:
https://clinicaltrials.gov/ct2/show/NCT02794350?term=NCT02794350&rank=1

TITLE: Characterization of Auditory Processing Involved in the Encoding of Speech Sounds (PRODIPRICIDE)
CT.gov ID: NCT02574299
Responsible Party: Hospices Civils de Lyon
Target Condition(s): Language Impairment, Hearing Loss
Intervention: Other: E-learningDevice: Hearing aids fitting
Phase: Not applicable
Study Start Date: October 2014
Description Provided: The ability to encode the speech signal is determined by ascending and descending auditory processing. Difficulties in processing these

speech signals are well described at the behavioral level in a specific language disorder. However, little is known about the underlying pathophysiological mechanisms. The assumption is that we should observe a degradation of the signal provided by the ear in the deaf subject while in case of specific language impairment it would be a phonemic disorder (possibly linked to a processing disorder auditory). The two population groups should therefore have different abnormalities of their central auditory process - which could be modified by the target remediation for each group.
URL:
https://clinicaltrials.gov/ct2/show/NCT02574299?term=NCT02574299&rank=1

TITLE: Evaluation of New Custom Made Hearing Product Technology and Shell Modification (CPS)
CT.gov ID: NCT02545569
Responsible Party: Phonak AG, Switzerland
Target Condition(s): Hearing Loss, Bilateral or Unilateral
Intervention: Device: hearing aid (MD class IIa) - ITE, BTE, RIC
Phase: Not applicable
Study Start Date: January 2017
Description Provided: The purpose of this evaluation is to receive the greatest benefit of new custom made hearing product technology and shell modification for the end customer and to continual improve the custom made hearing products.
URL:
https://clinicaltrials.gov/ct2/show/NCT02545569?term=NCT02545569&rank=1

TITLE: Cochlear Implantation for Treatment of Single-sided Deafness
CT.gov ID: NCT02532972
Responsible Party: Dr. Daniel Lee
Target Condition(s): Total Unilateral Deafness, Unilateral Partial Deafness
Intervention: Med-el MAESTRO Cochlear Implant with Flex 28 electrode array
Phase: Not applicable
Study Start Date: September 2015
Description Provided: This is a research study to determine whether a cochlear implantation (CI) device can improve hearing in people who are deaf in one ear (known as single-sided deafness).
URL:
https://clinicaltrials.gov/ct2/show/NCT02532972?term=NCT02532972&rank=1

TITLE: Effects of Cognitive Training on Speech Perception
CT.gov ID: NCT02294812
Responsible Party: Aaron Newman
Target Condition(s): Hearing Loss, Deafness and Auditory Perception
Intervention: Behavioral: Cognitive training
Phase: Not applicable
Study Start Date: September 2016
Description Provided: In this study, the investigators are testing whether cognitive training can lead to improvements in speech perception for individuals with hearing loss. Individuals will complete 20 hours of cognitive training that is designed to improve cognitive abilities such as short term memory and attention. The investigators predict that cognitive training that improves the cognitive abilities affected by hearing loss will improve speech perception.
URL:
https://clinicaltrials.gov/ct2/show/NCT02294812?term=NCT02294812&rank=1

TITLE: Cochlear Implants for Adults With Single-sided Deafness (SSD)
CT.gov ID: NCT02259192
Responsible Party: Robert Shannon
Target Condition(s): Single-sided Deafness
Intervention: Device: MED-EL Maestro Cochlear Implant
Phase: Not applicable
Study Start Date: September 2014
Description Provided: The purpose of this investigation is to determine the safety and preliminary efficacy of implanting a cochlear implant (CI) in the profoundly deaf ear of an adult with one normal hearing (NH) ear (termed "single-sided deaf" person, or SSD). The potential subjects will have been deafened post-lingually, thus, at one point the now deafened ear did conduct sound from the periphery. The MED-EL CI system will be implanted in ten (10) SSD patients.The long-term goal of this research program is to determine whether the CI, in combination with the NH ear, may provide improved localization ability and better speech understanding in noise, relative to performance before cochlear implantation (i.e., with the NH ear alone). A secondary long-term goal is to determine whether CI stimulation may reduce tinnitus severity, compared to tinnitus experienced prior to cochlear implantation or when the CI is turned off, after implantation.
URL:
https://clinicaltrials.gov/ct2/show/NCT02259192?term=NCT02259192&rank=1

TITLE: Cochlear Implantation in Single Sided Deafness and Asymmetrical Hearing Loss: a Cost/Utility Study. (CISSD)
CT.gov ID: NCT02204618
Responsible Party: University Hospital, Toulouse
Target Condition(s): Retrocochlear Pathology, Auditory Processing Disorder, Central, Major Cochlear Ossification or Malformation
Intervention: Device: cochlear implantation, Other: 6 months initial abstention
Phase: Not applicable
Study Start Date: October 2014
Description Provided: The investigators assume that cochlear implants in this indication are not only effective but also cost-effective. The investigators' experimental protocol relies on real life therapeutic strategy, where a cochlear implant may be proposed once CROS and bone conductions systems have failed. Thus, all subjects enrolled in our study will try CROS and bone conduction devices. If these trials are ineffective, the remaining subjects will be randomized between two arms (cochlear implantation vs 6 months abstention followed by cochlear implantation). A comparative cost-utility analysis between the two arms, of medical consequences measured in terms of quality of life will identify a preference for a strategy. Specific binaural hearing measurements with respect to each treatment option (abstention, CROS, bone conduction device, cochlear implant) will also be collected.
URL:
https://clinicaltrials.gov/ct2/show/NCT02204618?term=NCT02204618&rank=1

TITLE: Cochlear Implantation in Cases of Single-Sided Deafness (CI in SSD)
CT.gov ID: NCT02203305
Responsible Party: University of North Carolina, Chapel Hill
Target Condition(s): Unilateral Moderate to Profound Hearing Loss, Single-Sided Deafness (SSD), Asymmetric Hearing Loss
Intervention: Device: Cochlear ImplantOther: Control Group
Phase: Not applicable
Study Start Date: October 2014
Description Provided: The primary goal of this project is to determine whether subjects with Single-Sided Deafness (SSD) experience an improvement in speech perception, localization, and quality of life with a cochlear implant as compared to an unaided listening condition.
URL:
https://clinicaltrials.gov/ct2/show/NCT02203305?term=NCT02203305&rank=1

TITLE: NAC to Prevent Cisplatin-induced Hearing Loss
CT.gov ID: NCT02094625
Responsible Party: Children's Hospital Los Angeles
Target Condition(s): Neuroectodermal Tumors, PrimitiveLiver Neoplasms, Osteosarcoma, Other Childhood Cancers Using Cisplatin-based Regimens
Intervention: Drug: N-Acetylcysteine
Phase: 1
Study Start Date: March 2015
Description Provided: Cisplatin is a key chemotherapy agent for the treatment of multiple childhood cancers but causes permanent hearing loss. This study investigates the drug N-acetylcysteine (NAC) to determine the dose necessary to protect hearing and also how well tolerated NAC is when combined with chemotherapy.
URL:
https://clinicaltrials.gov/ct2/show/NCT02094625?term=NCT02094625&rank=1

TITLE: Latanoprost for the Treatment of Menière's Disease
CT.gov ID: NCT01973114
Responsible Party: Synphora AB
Target Condition(s): Menière's Disease
Intervention: Drug: Latanoprost, Other: Placebo
Phase: 2
Study Start Date: October 2013
Description Provided: The purpose of the study is to evaluate the dose regimen, efficacy and safety of latanoprost for the treatment of Menière's disease.
URL:
https://clinicaltrials.gov/ct2/show/NCT01973114?term=NCT01973114&rank=1

TITLE: Investigation of Anatomical Correlates of Speech Discrimination
CT.gov ID: NCT01781039
Responsible Party: Steward St. Elizabeth's Medical Center of Boston, Inc.
Target Condition(s): Sensorineural Hearing Loss
Intervention: Not specified
Phase: Not specified
Study Start Date: January 2013
Description Provided: Understanding speech is essential for good communication. Individuals with hearing loss and poor speech discrimination often have little success with hearing aids because amplifying sound improves audibility, but not clarity of the speech signal. The purpose of this study is to

determine the relative importance of the sensory cells of the inner ear and auditory neurons on speech discrimination performance in quiet and in noise. This information may be used as a predictor of hearing aid benefit. The investigators expect to find decreased speech understanding ability resulting from both loss of sensory cells and the loss of auditory neurons.
URL:
https://clinicaltrials.gov/ct2/show/NCT01781039?term=NCT01781039&rank=1

TITLE: Daily Exposure Monitoring to Prevent Hearing Loss (DEMON)
CT.gov ID: NCT01714375
Responsible Party: Yale University
Target Condition(s): Hearing Loss
Intervention: Device: QuietDose Device
Phase: 2
Study Start Date: July 2007
Description Provided: The goal of this study is to determine whether daily assessment and feedback of workers' noise exposures leads to more effective use of hearing protection and prevention of noise-induced hearing loss.
URL:
https://clinicaltrials.gov/ct2/show/NCT01714375?term=NCT01714375&rank=1

TITLE: Transtympanic Ringer's Lactate for the Prevention of Cisplatin Ototoxicity
CT.gov ID: NCT01108601
Responsible Party: McGill University Health Center
Target Condition(s): hearing loss
Intervention: Drug: Ringer's Lactate (0.03% Ciprofloxacin)
Phase: 1 & 2
Study Start Date: April 2008
Description Provided: Cisplatin and carboplatin induce ototoxicity manifested as sensorineural hearing loss, tinnitus, and/or vestibular disturbances. Ototoxicity is induced via damage to inner ear structures by reactive oxygen species. Previous animal studies demonstrated that transtympanic injection of Ringer's Lactate (RL) provided near complete otoprotective effect against cisplatin. The purpose of this study is to determine if transtympanic administration of Ringer's Lactate via a pressure equalising (PE) tube in patients undergoing platinum based chemotherapy treatment will prevent tinnitus, vestibular dysfunction and hearing loss especially at high frequencies. Pre- and post- chemotherapy

treatment audiometry will be measured and statistically analysed for significance.
URL:
https://clinicaltrials.gov/ct2/show/NCT01108601?term=NCT01108601&rank=1

TITLE: Clinical Study of Muenke Syndrome (FGFR3-Related Craniosynostosis)
CT.gov ID: NCT00106977
Responsible Party: National Human Genome Research Institute (NHGRI)
Target Condition(s): Craniosynostosis, Muenke Syndrome
Intervention: Not specified
Phase: Not specified
Study Start Date: March 31, 2005
Description Provided: Craniosynostosis is a common craniofacial abnormality caused by premature fusion of one or several sutures of the skull. The prevalence of craniosynostosis is approximately 1 in 2,100 to 3,000 births. Originally described by our group, Muenke syndrome (OMIM # 602849) is a specific form of craniosynostosis caused by a single nucleotide transversion in fibroblast growth factor receptor 3 (FGFR3), c.749C>G, resulting in p.Pro250Arg. Individuals carrying the defining mutation variably manifest coronal suture craniosynostosis, developmental delay, deafness, and carpal and tarsal bone fusion. The purpose of the present study is to increase our understanding of the clinical manifestations of Muenke syndrome through detailed physical, developmental, neurologic, dental, ophthalmologic, otolaryngologic, audiologic, radiologic, and genetic/genomic studies. We also plan to examine the spectrum of clinical characteristics of Muenke syndrome to facilitate early diagnosis and clinical management, including genetic counseling. To accomplish this, we plan to enroll approximately 10-20 probands, as well as their family members each year, with an enrollment ceiling of 200 probands. Our study has three arms. The clinical arm is the major focus of our study. Patients and their families will be seen at the NIH Clinical Center and Children's National Medical Center. Individuals with Muenke syndrome who are unable or unwilling to come to the NIH, can submit their medical records, including a copy of the molecular testing, for review. The second arm is genetic/genomic studies with the goal of investigating modifying factors that relate to disease severity and expression. The third arm consists of a cognitive function, development and hearing questionnaire to be completed by patients online, via phone or mail.
URL:
https://clinicaltrials.gov/ct2/show/NCT00106977?term=NCT00106977&rank=1

TITLE: Genetic Analysis of Hereditary Disorders of Hearing and Balance
CT.gov ID: NCT00023049
Responsible Party: National Institute on Deafness and Other Communication Disorders (NIDCD)
Target Condition(s): Sensorineural Hearing Loss, Hearing Disorder, Vestibular Disease
Intervention: Not applicable
Phase: Not applicable
Study Start Date: August 20, 2001
Description Provided: Hereditary hearing impairment is a genetically heterogeneous disorder that can be caused by mutations in any one of hundreds of different genes. Approximately 20 genes have now been identified in which mutations can cause nonsyndromic sensorineural hearing loss. The identification and analysis of these genes and their mutations are providing critical insights into the development, structure, and function of the auditory system, as well as the molecular mechanisms associated with disruption of these processes. In contrast, the molecular mechanisms underlying familial disorders affecting peripheral vestibular function appear to be more rare, have not been well described, and are less well understood. The peripheral auditory and vestibular systems share many common features in both health and disease, and many hereditary hearing loss disorders also affect vestibular function. The purpose of this study is to identify genes and mutations causing hereditary disorders of hearing, balance, or both. Members of families segregating hereditary disorders of hearing or balance will be enrolled in the proposed study in order to: (1) define and characterize the phenotypes and natural histories; (2) identify the underlying causative mutations and genes by linkage, positional cloning, and/or candidate gene mutation analyses; (3) and correlate observed phenotypes with the corresponding mutations and functions of the underlying genes.
URL:
https://clinicaltrials.gov/ct2/show/NCT00023049?term=NCT00023049&rank=1

TITLE: Clinical and Genetic Analysis of Enlarged Vestibular Aqueducts
CT.gov ID: NCT00023036
Responsible Party: National Institute on Deafness and Other Communication Disorders (NIDCD)
Target Condition(s): Sensorineural Hearing LossCytomegalovirus Infection
Intervention: Not specified
Phase: Not specified

Study Start Date: August 17, 2001
Description Provided: Nonsyndromic hereditary hearing impairment is a genetically heterogeneous disorder that can be caused by mutations in any one of at least 60 different genes. Enlargement of the vestibular aqueduct (EVA) is a radiologic finding known to be associated with mutations in one of these genes, the Pendred syndrome gene (SLC26A4, formerly known as PDS). EVA may thus serve as a clinically useful marker to facilitate the diagnosis of hearing impairment. Recent data from our laboratory and others indicates that only a subset of individuals with EVA have SLC26A4 mutations, and therefore some EVA cases are likely to be caused by other genes, nongenetic factors, or a combination of these etiologies. Families with two or more individuals with hearing impairment and EVA will be enrolled in this study in order to identify other genetic factors that cause EVA. Siblings and parents may also be enrolled in order to define inheritance and to perform molecular genetic analyses.
URL:
https://clinicaltrials.gov/ct2/show/NCT00023036?term=NCT00023036&rank=1

https://hearing.health.mil/Research/PIHL-Working-Group/PIHL-Newsletters

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