Ototoxicity and Noise Damage: Translating Preclinical Findings to Audiological Management
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Welcome to the 2019 NCRAR biennial conference on Ototoxicity and Noise. This conference program contains information about the conference location, daily schedule, social events and details about our distinguished group of speakers. We are enthusiastic to have a diverse program focused on cutting-edge research in the areas of ototoxicity and noise-related damage, as well as clinical representation of how the impact from these exposures may result in auditory impairments and reduced quality of life.

Over the coming three days, you will learn about the mechanisms and models of noise-induced hearing loss and ototoxicity (Day 1), the clinical presentations of these insults (Day 2), and technological advancements in diagnostics or therapeutic developments (Day 3).

Several aspects of the conference facilitate knowledge translation to [and from] patient care. Day 1 describes the many challenges and opportunities in going from animal to human models. Day 2 includes a session designed to place the physical symptoms of these auditory injuries in the context of the whole person by providing several patients’ perspectives. Day 3 provides an opportunity to collaboratively discuss strategies for optimizing health function and rehabilitation outcomes with input from an array of stakeholders. The conference closes with interactive sessions focused on practical considerations for a successful ototoxicity management program; and issues related to the exchange of hearing health care information between the Department of Defense (DoD) and the Department of Veterans Affairs (DVA).

We anticipate you’ll take away valuable information to apply to your work – whether that be in clinical practice, teaching or research. We encourage conference attendees to facilitate discussions with colleagues and students, so we can disseminate the information learned to others in the field.

Our Program Committee, led by Co-Chairs Naomi Bramhall and Angela Garinis, benefitted from the expert input of our Center Director, Patrick Feeney and Keynote Speakers, Sharon Kujawa and Peter Steyger. On a personal level, we are extremely grateful to Christine Kaelin, Conference Coordinator, who has spent countless hours planning the logistical aspects of the meeting, for helping facilitate the patient videos, and for doing the paperwork to enable us to provide you with ASHA and AAA CEUs. We also thank our sponsors whose generous support enables us to host this meeting (see Page 4 of this program).

We hope to have a chance to meet all of you over the coming few days, such as at the Poster Session on Wednesday the 25th, at the networking dinner on Thursday the 26th, during the small group discussions on Friday the 27th, or during the breaks.

We hope you enjoy the conference and can immerse yourself in the culture and scenic beauty of the Portland area while you are here. Make sure to walk around the city – or to use public transport – it’s the Portland way.

Yours,

Conference Chair & NCRAR Associate Director:...........Dawn Konrad-Martin
Program Co-Chairs:.....................................................Naomi Bramhall and Angela Garinis
NCRAR Director..........................................................Patrick Feeney
Conference Sponsors

The NCRAR thanks the following organizations and businesses for their generous sponsorship of the conference:

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CONFERENCE SCHEDULE
Ototoxicity and Noise Damage: Translating Preclinical Findings to Audiological Management

PROGRAM FOR THE NCRAR BIENNIAL CONFERENCE, SEPTEMBER 25-27, 2019

WEDNESDAY, SEPTEMBER 25TH (FULL DAY 7:15AM – 5:00PM)

Mechanisms and Models

7:15 – 7:45am Registration and light continental breakfast
7:45 – 8:00am Welcome and introductions. Dawn Konrad-Martin PhD, Naomi Bramhall, PhD and Angela Garinis, PhD
8:00 – 9:00am **Keynote: Mechanisms of Noise-Induced Hearing Loss**, Sharon Kujawa, PhD
9:00 – 10:00am **Keynote: Mechanisms of Aminoglycoside- and Cisplatin-Induced Ototoxicity**, Peter Steyger, PhD
10:00 – 10:30am BREAK
10:30 – 11:20am **Central Consequences of Peripheral Damage**, Richard Salvi, PhD
11:20am – 12:10pm **Statistical Modeling Approaches Studying Ototoxicity-Induced Hearing Loss**, Garnett McMillan, PhD
12:10 – 1:45pm LUNCH BREAK
1:45 – 2:35pm **Epidemiological and Statistical Modeling Approaches Studying Noise-Induced Hearing Loss**, Martin Slade, MPH
2:35 – 3:00pm Poster setup/BREAK
3:00 – 5:00pm Poster Session and “Meet the Scientist.” Refreshments will be served. 3rd Floor World Trade Center

THURSDAY, SEPTEMBER 26TH (FULL DAY 7:15AM – 5:00PM)

Clinical Presentations of Noise-Induced Hearing Loss and Ototoxicity

7:15 – 7:45am Registration and light continental breakfast
7:45 – 8:00am Introductions
8:00 – 8:50am **Evidence of Cochlear Synaptopathy in Young Veterans**, Naomi Bramhall, PhD
8:50 – 9:40am **Risk Factors for Developing Occupational Noise-induced Hearing Loss**, Wei Qiu, PhD
9:40 – 10:10am BREAK
10:10 – 11:00am **Impacts of Blast Exposure on the Central Auditory System**, Melissa Papesh, AuD PhD
11:00 – 11:50am **Epidemiologic approaches to examining noise exposure and other risk factors for tinnitus**, Sarah Theodoroff, PhD and Kelly Reavis, MPH, MS
11:50am – 1:15pm LUNCH BREAK
1:15 – 2:05pm **Ototoxicity of Aminoglycosides in Patients with Cystic Fibrosis**, Angela Garinis, PhD and Lisa Hunter, PhD
2:05 – 2:55pm **Ototoxicity of Chemotherapeutic Agents**, Kristin Knight, M.S. and Dawn Konrad-Martin, PhD
2:55 – 3:30pm BREAK
3:30 – 4:20pm **Military Ototoxic Solvent Exposures and the Interaction with Noise Exposure**, William Murphy, PhD
4:20 – 5:00pm **Patient Perspectives Presentations**, Videotaped and interactive patient testimonials
6:30 – 10:00pm Informal Networking Dinner: Lola’s Room/McMenamin’s, 1332 W Burnside St, Portland, OR 97205

FRIDAY, SEPTEMBER 27TH (7:15AM – 2:30PM)

Future Directions

7:15 – 7:45am Light continental breakfast
7:45 – 8:00am Introductions
8:00 – 8:50am **Regeneration of Hair cells, Synapses, and Neurons**, Albert Edge, PhD
8:50 – 9:40am **Preventing Ototoxicity with Otoprotectants**, Jian Zuo, PhD
9:40 – 10:10am BREAK
10:10 – 11:00am **Using Computational Models for Differential Diagnoses of Sensory vs. Neural Damage**, Sarah Verhulst, PhD
11:00am – 12:30pm Panel Discussion on Interdisciplinary, Inter-Agency Perspectives on Patient Management
12:30 – 1:00pm BREAK/Box lunch
1:00 – 2:30pm **Breakout sessions: Practical Implementation Issues**, LaKeisha Henry, Col., MD, PhD; Kelly Reavis, MPH, Carmen Brewer, PhD, Evie Ortiz, AuD, Wendy Landier, PhD
Stephen A. Fausti Scholarship
Dr. Fausti’s foundational research on ototoxicity and high frequency hearing damage with noise were an inspiration for this conference, and so it is in his honor that we provide this scholarship.

Recipient: Michael Doing (pictured on the right), AuD Student at University of Minnesota

Mr. Doing was selected for this award as the applicant best characterizing special insight, strategies or solutions for addressing the real-life impacts of hearing loss, tinnitus or balance research.

About Mr. Doing: Michael Doing is an audiology extern with a unique insight into hearing healthcare and the role of hearing loss prevention. He has taken ototoxic medications throughout his lifetime for the treatment of cystic fibrosis, and has been exposed to recreational noise without hearing protection. Although his hearing is considered borderline normal, Mr. Doing experiences numerous auditory challenges. These include difficulty hearing in noise, and living with constant, bilateral, bothersome tinnitus. Mr. Doing is passionate about providing his perspective on the role of the audiologist in complex patient care, and barriers to providing best-practice ototoxicity monitoring, and the importance of counseling and educating patients sufficiently and appropriately.

He will be providing his views as an audiology student and a person with auditory damage associated with exposure to ototoxins and noise, as part of an interactive session on the patient’s perspective (Thursday, 4:20 – 5:00pm).

About Dr. Fausti:

NCRAR’s founder, Dr. Stephen (Steve) Fausti founded the NCRAR back in 1997. He retired in 2010, after dedicating 39 years to VA and holding the distinction of being one of the longest continuously-funded VA investigators.

Dr. Fausti’s inspiration for founding the NCRAR was to build an auditory research center that had the capacity to attract and cultivate exceptional auditory researchers at all stages in their career – from students to senior scientists. This model remains in place today. His plan for the Center was simple: hire staff with diverse yet complementary expertise, and a deep-seated commitment to our core mission, so that the whole could become greater than the sum of its parts. The NCRAR has been on the cutting edge of auditory rehabilitation research in the areas of early identification of ototoxic-induced hearing loss, tinnitus evaluation and treatment, central auditory processing disorders associated with traumatic brain injury and/or blast exposure, effects of diabetes and multiple sclerosis on auditory function, hearing loss prevention, health behavior change, and many others. This conference is one of many ways in which NCRAR keeps its commitment to serve as a national resource for auditory research and clinical care.

Going forward, Dr. Fausti’s hope is that the Center continues to grow and remains a premier translational research facility and a magnet for international collaborators who generate quality research with clinical application to auditory rehabilitation. In this way he hopes it can fulfill its mission of “alleviating communicative disorders that result from auditory system impairments in Veterans as well as the general public.”
Presenters and Abstracts
Wednesday, September 25th morning sessions

Keynote Address: Mechanisms of Noise-Induced Hearing Loss
Sharon Kujawa, PhD
Wednesday, 8:00 – 9:00am

About Dr. Kujawa:
Sharon G. Kujawa, Ph.D., serves on the faculty of the Department of Otolaryngology-Head and Neck Surgery, Harvard Medical School. She is the Director of Audiology Research and a Senior Scientist in the Eaton-Peabody Laboratories, Massachusetts Eye and Ear, Boston, MA. She is on the adjunct faculty of the Program in Speech and Hearing Biosciences and Technology at Harvard University. Dr. Kujawa is an auditory neuroscientist and clinician whose research seeks to clarify mechanisms and consequences of common causes of acquired sensorineural hearing loss and to translate that knowledge into improved diagnosis and treatments that benefit people. A major focus of her current work is in understanding how sound overexposure and aging cause loss of cochlear hair cell – nerve fiber communications (synapses), determining the functional consequences of that loss and how it is shaped by sensory cell damage, and clarifying how the degeneration can be manipulated pharmacologically to reveal mechanisms and provide treatments.

Presentation Overview:
Noise-induced hearing loss results when exposure to damaging levels of sound injures delicate inner ear structures and compromises vulnerable inner ear functions. The noise-induced threshold sensitivity loss captured by the audiogram can be temporary or permanent, and the underlying injury, subtle or dramatic. Permanent threshold losses after noise are associated with permanent cochlear injury, often hair cell damage or loss. Beyond these well-established effects of noise, widespread and progressive cochlear synaptic and neural losses are now well recognized, occurring even when thresholds recover in the short term. The focus of this talk is on acute, chronic, and delayed effects of noise on the ear and hearing. In its description of these outcomes, and of the factors that can shape them, it relies heavily on animal models, as these provide the opportunity for strict experimental control and access to underlying histopathology. With improved understanding of processes and pathology instigated by noise come possibilities for better-informed translation. The talk thus considers opportunities and challenges to the translation of experimental findings in animal models to the diagnosis, treatment and prevention of noise-induced hearing loss and cochlear injury in humans.

Funding support: Dr. Kujawa’s research is supported by the National Institutes of Health (NIH) National Institute on Deafness and Other Communication Disorders (NIDCD; P50DC015857), the Department of Defense and the Office of Naval Research.
Keynote Address: Mechanisms of Aminoglycoside- and Cisplatin-Induced Ototoxicity

Peter Steyger, PhD
Wednesday, 9:00 – 10:00am

About Dr. Steyger:

Peter Steyger, Ph.D., is the inaugural director of the Translational Hearing Center in the Department of Biomedical Sciences at Creighton University School of Medicine. At the age of three, Dr. Steyger attended the University of Manchester, England to learn to listen and speak following drug-induced hearing loss as a consequence of aminoglycoside treatment for bacterial meningitis. He subsequently obtained a bachelor’s degree in Zoology at the University of Manchester in 1984, followed by a Ph.D. in Communications and Neuroscience at Keele University, England. After postdoctoral training in vestibular neurosciences in San Antonio, Texas and the Neurological Sciences Institute in Portland Oregon, Dr. Steyger joined the Oregon Hearing Research Center at Oregon Health & Science University in 1997. In June 2019, he moved into his current position at Creighton University. He has two current R01 awards that focus on (i) identifying mechanisms of aminoglycoside-induced ototoxicity and (ii) translating that knowledge to clinical populations that can lead to refined clinical care guidelines for improved otoprotective strategies that better prevent drug-induced cochleotoxicity.

Presentation Overview:

Acquired hearing loss from hospital-prescribed medications affect as many as 1 million people each year in Western Europe and North America. However, there are no current federally-approved drugs to prevent or treat the debilitating and permanent hearing loss caused by life-saving platinum-based anticancer drugs or bactericidal aminoglycoside antibiotics. Hearing loss has long-term impacts on quality-of-life measures, especially in young children and older adults. This talk will review our current understanding of the mechanisms underlying drug-induced hearing loss and highlight the gaps that remain. Challenges in translating this knowledge into the clinic, and in developing, or re-purposing, therapeutics to prevent drug-induced hearing loss will also be addressed.

Funding support: Dr. Steyger’s research is supported by NIH-NIDCD (DC004555, DC012588, DC016680).
Central Consequences of Peripheral Damage
Richard Salvi, PhD
Wednesday, 10:30 – 11:20am

About Dr. Salvi:
Richard Salvi, Ph.D., is a SUNY Distinguished Professor in the Department of Communicative Disorders and Science and is the Director for the Center for Hearing and Deafness at the University at Buffalo. Dr. Salvi received his Ph.D. in Experimental Psychology from Syracuse University and completed a Post-Doctoral Fellowship at Upstate Medical Center in Syracuse, NY. He has a long-standing interest in noise-induced hearing loss, ototoxicity, aging, tinnitus, hyperacusis, functional brain imaging, neuroplasticity, cell death, regeneration and otoprotection. He has served on many editorial boards, grant review panels and advisory boards.

Presentation Overview:
Cochlear damage from ototoxic drugs, noise exposure, and aging can greatly reduce the neural activity flowing from the auditory nerve into the central nervous system. In a simple linear system, the lack of neural input would be expected to cause suprathreshold sounds to seem muffled or less salient. However, neuroplastic changes along the central auditory pathway amplify and compensate for the reduced neural input from the cochlea by turning up the gain at multiple stages along the central auditory pathways so that by the time the signal reaches the auditory cortex, neural responses can be equal to or much larger than normal, a phenomenon often referred to as Enhanced Central Gain. I will describe dramatic changes in enhanced gain that can occur both within the central auditory pathway as well as in several structures outside the classical auditory pathway following noise or drug-induced damage to the cochlear hair cells and auditory nerve fibers. While Enhanced Central Gain can make weak sounds more audible or salient, excessive central gain could contribute to tinnitus, loudness recruitment, and hyperacusis. Funding support: Dr. Salvi’s work is supported by NIH-NIDCD (5R01DC006630, R01DC009091, R01DC009219, R01DC011808).

Statistical Modeling Approaches Studying Ototoxicity-Induced Hearing Loss
Garnett McMillan, PhD
Wednesday, 11:20am – 12:10pm

About Dr. McMillan:
Garnett McMillan, Ph.D., is a NCRAR Biostatistician, Clinical Assistant Professor in the Department of Public Health and Preventive Medicine at Oregon Health & Science University, and Adjunct Assistant Professor in the Department of Anthropology at the University of New Mexico. Dr. McMillan received his Ph.D. in Biological Anthropology and M.S. in Mathematics and Statistics from the University of New Mexico. After completing a post-doctoral fellowship in cancer epidemiology with the World Health Organization, Dr. McMillan joined the NCRAR in 2008 and has focused on statistical methods in diagnostic test development, patient screening, psychoacoustics, and audiological epidemiology. Dr. McMillan has published on diverse topics in human biology, conservation biology, cancer epidemiology, clinical audiology, and speech and hearing research as well as statistical theory and practice.

Presentation Overview:
A long-standing goal in auditory research is to identify sources of variation in ototoxic effects and to accurately predict hearing change in patients prescribed with a particular treatment regimen. There are currently a wide variety of approaches for evaluating treatments and risk factors for ototoxicity, and for ototoxicity forecasting. However, current methods do not easily permit extrapolation to new or different treatment schedules, and do not generalize to audiological outcomes that vary among stakeholders. This talk describes the statistical development of a new approach to ototoxicity modeling that overcomes existing limitations and is easily generalized to any type of ototoxic exposure or outcome measure.
Epidemiological and Statistical Modeling Approaches Studying Noise-Induced Hearing Loss

Martin Slade, MPH
Wednesday, 1:45 – 2:35pm

About Mr. Slade:

Martin Slade, M.P.H., is the Director of Research for Yale University Occupational & Environmental Medicine as well as co-director of Yale University Maritime Research Center. He moved to academia after a successful career as the Product Development Assurance Manager at AlliedSignal Corporation, where he developed statistical methodology to evaluate the performance of gas turbine engines. Throughout the last 17 years, he has focused on the development of study designs and analytical methods to evaluate occupational, environmental, psychosocial and genetic determinants of disease as well as the safety and efficacy of treatment. A primary focus of his research has been on interventions for prevention and treatment of both mild traumatic brain injury as well as noise-induced hearing loss. He has worked with the Department of Defense, including the Hearing Center of Excellence, for over a decade and has been the primary biostatistician for many research activities including clinical trials of pharmaceutical interventions for hearing loss and mild traumatic brain injury.

Presentation Overview:

Despite government mandated interventions, occupational noise-exposure is a significant problem often resulting in permanent hearing loss. Evidence-based research is limited in providing standards about an optimal research methodology to investigate and interpret industry-related studies of noise induced hearing loss. This talk will discuss how study design impacts noise-induced hearing loss research. Specifically, the presentation will cover the importance of a standard definition of noise exposure, the complexities involved in defining an individual’s hearing status when pure tone thresholds are measured across multiple frequencies and two ears, and how to develop a statistical model that can handle these types of data. The development of analytical models to evaluate the effects of physical and psychosocial factors on the patterns of disease and injury within industrial workplaces is critical to understanding the impact of long-term noise exposure on one’s health. A greater understanding of the physical quality of noise, the evaluation of hearing sensitivity in a given cohort and the selection of an appropriate statistical model is instrumental to developing an optimal research strategy for evaluating risk.
**Evidence of Cochlear Synaptopathy in Young Veterans**

*Naomi Bramhall, PhD*

Thursday, 8:00 – 8:50am

**About Dr. Bramhall:**

Naomi Bramhall, Au.D. Ph.D., is a Research Investigator at the NCRAR, clinical audiologist for the VA Portland Health Care System, and Assistant Professor of Otolaryngology/Head and Neck Surgery at Oregon Health & Science University. She received her B.S. in Biology from McGill University and a B.S., M.S., and Au.D. in Speech and Hearing Sciences at the University of Washington. As a Ph.D. student in the Harvard-MIT Program in Speech and Hearing Bioscience and Technology, she studied hair cell regeneration with Dr. Albert Edge. She then worked as a clinical audiologist for 1.5 years before joining the NCRAR in 2014. Her research focuses on noise-induced hearing loss in Veterans, with an emphasis on noise-induced cochlear synaptopathy.

**Presentation overview:**

Cochlear synaptopathy, the partial loss of auditory nerve synapses onto inner hair cells, has been proposed as a possible source of hyperacusis, some forms of tinnitus, and difficulty understanding speech in background noise. In animal models, cochlear synaptopathy is associated with a reduction in the amplitude of wave I of the auditory brainstem response (ABR) and can occur even when auditory thresholds are normal. This talk will present evidence of noise exposure-related changes to several auditory physiological measures, including the ABR, in young military Veterans with clinically normal pure tone thresholds. Although noise-induced synaptic loss is difficult to separate from outer hair cell damage, Veterans differ from non-Veteran controls on these physiological measures even after statistically adjusting for sex and otoacoustic emissions, suggestive of synaptic or neuronal loss. While these physiological changes do not appear to be related to decreased performance on standard speech-in-noise tests, they are associated with increased central gain and the report of tinnitus. Although post-mortem histological analysis would be necessary for confirmation, these data are consistent with animal models of cochlear synaptopathy and suggest that synaptic loss occurs in response to high intensity noise exposure in humans and is correlated with tinnitus.

*Funding Support:* Dr. Bramhall’s research is supported by the VA RR&D (Career Development Awards #C1484-M, #C2104-W, Center Award #C9230-C, and Merit Review Award #C7450-R) and the Department of Defense (W81XWH-15-1-01-3).

**Risk Factors for Developing Occupational Noise-Induced Hearing Loss**

*Wei Qiu, PhD*

Thursday, 8:50 – 9:40am

**About Dr. Qiu:**

Wei Qiu, Ph.D., is a Senior Research Scientist and the Director of Auditory Research Laboratory, State University of New York at Plattsburgh. He holds a B.S. degree in Biomedical Engineering and a Ph.D. in Electronic Engineering. He has worked in the area of noise effects and hearing conservation for 20 years. Dr. Qiu is one of the researchers who originally introduced the idea of using the kurtosis as an index of the hazard to hearing from noise exposures. He published a series of articles exploring the use of kurtosis metric to predict noise-induced hearing loss in the animal and human models. His current research efforts are aimed to complex noise-induced hearing loss, noise-induced cochlear synaptopathy, and combined effects of co-exposure to solvents and noise.
Presentation Overview:
Although the ISO-1999 document is currently the most accepted noise damage-risk criterion, research has shown it to be inadequate. Controversy exists over not only the accuracy of the epidemiological data used to derive ISO-1999, but also over its ability to estimate hearing loss in individuals. The fundamental problem with this and other exposure criteria is their reliance on an energy metric to quantify an exposure, which completely ignores the effects of temporal variables known to be important in affecting noise-induced hearing loss (NIHL). A variety of experiments in animals that have shown that in addition to energy, the statistical metric of the amplitude distribution (kurtosis) is necessary for the characterization of non-Gaussian complex noise. Recently, an investigation was conducted in collaboration with the Chinese Center for Disease Control and Prevention on occupational NIHL in China. Audiometric and noise exposure data were acquired on a population (N=2,333) of screened workers from 34 industries in China. Results from these studies in animal models and in humans have shown that the kurtosis may be a necessary metric for predicting the risk of hearing loss from complex noise. These studies demonstrated the following: 1) The ISO-1999 prediction model underestimated hearing trauma by complex noise; 2) an energy metric (Leq) alone is not sufficient to characterize a complex noise and that the kurtosis, along with Leq, is necessary for the prediction of NIHL associated with complex noise; 3) for the same exposure level, the prevalence of high-frequency NIHL is greater in workers exposed to non-G noise environments than for workers exposed to G noise, 4) the kurtosis ordered the extent of hearing trauma, i.e., for a fixed energy level, the noise-induced trauma increased as the kurtosis increased. These findings indicate that the applicability of the ISO-1999 prediction model to different types of noise exposures needs to be carefully re-examined.

Funding Support: Dr. Qiu’s research is supported by NIH-NIDCD and NIH-NIOSH (200-2015-M-63857, 200-2016-M-91922 from NIOSH; N00014-17-1-2198 from DoD Office of Naval Research; 1R01DC015990-01).

Impacts of Blast Exposure on the Central Auditory System
Melissa Papesh, PhD
Thursday, 10:10 – 11:00am

About Dr. Papesh:
Melissa Papesh, Au.D. Ph.D., is a Research Investigator at the NCRAR and an Assistant Professor of Otolaryngology/Head and Neck Surgery at Oregon Health & Science University. She received an Au.D. and a dual Ph.D. in Hearing Science and Neural Science from Indiana University, as well as a postdoctoral Advanced Research Fellowship in Polytrauma and Traumatic Brain Injury Rehabilitation awarded by the VA Office of Academic Affiliations. Her research focuses on diagnosis and rehabilitation of Veterans and Service Members with auditory processing disorders (APD). Over the past eight years at the NCRAR, she has focused on bringing together subjective, behavioral, and electrophysiological measurement techniques to assess alterations in central nervous system processing among patients with blast exposure, traumatic brain injuries and posttraumatic stress disorder (PTSD). She is also highly active in clinical and research domains related to APD across the VA, including as an active contributing member of the VA/DoD Auditory Processing Disorder Working Group and facilitator of an APD listserv for VA audiologists and speech-language pathologists involved in APD testing.

Presentation overview:
Military Veterans who have been exposed to high-intensity blast waves often experience auditory difficulties that persist long after the blast incident, even in the absence of hearing loss. The unprecedented use of improvised explosive devices in ongoing military conflicts has helped to fuel a substantial increase in the number of Veterans seeking help for auditory processing difficulties, as well as growing interest among VA audiologists in clinical assessment and management strategies for this population. Recent research reveals that many different types of processing deficits may arise following blast exposure, and that additional comorbid health factors are very common in this patient population. This presentation will review the unique nature of blast-exposure injuries and the complex factors that may underlie auditory processing deficits in the Veteran population, including potential associations with other comorbid
health factors such as post-traumatic stress disorder. This talk will discuss the findings from previous research studies exploring hearing-related outcomes following blast exposure as well as the current state of clinical care for these patients.

**Funding support:** Dr. Papesh’s research is supported by VA RR&D (CDA2 Award #C2673-W, and Merit Review Award C7755-I); VA OAA Advanced Research Fellowship in Polytrauma/TBI Rehabilitation; Oregon Clinical and Translational Research Institute (grant #UL1TR002369).

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### Epidemiologic approaches to examining noise exposure and other risk factors for tinnitus

**Sarah Theodoroff, PhD and Kelly Reavis, MPH, MS**

**Thursday, 11:00 – 11:50am**

**About Dr. Theodoroff:**
Sarah M. Theodoroff, Ph.D., is a Research Investigator at the NCRAR and an Assistant Professor of Otolaryngology/Head and Neck Surgery at Oregon Health & Science University. Dr. Theodoroff’s avenue of research is focused on improving the diagnosis, assessment, and treatment of auditory complaints that are not adequately evaluated by the standard test battery nor effectively treated. Her work aims to improve patient-centered clinical protocols and increase awareness of the needs of patients with tinnitus, hyperacusis, and other decreased sound tolerance disorders among medical professionals and the general public.

**About Ms. Reavis:**
Kelly M. Reavis, MS, MPH, is a Research Audiologist at the U.S. Department of Veterans Affairs, Rehabilitation Research and Development, National Center for Rehabilitative Auditory Research, located at the VA Portland Health Care System. She is also a PhD candidate in the Epidemiology program at Oregon Health & Science University-Portland State University School of Public Health. Her research interests are centered on the transfer of evidence-based protocols for the detection of hearing loss and tinnitus secondary to chemotherapeutic exposures from the laboratory to the clinic. Additionally, she is interested in identifying risk factors for, and the distribution of, auditory injuries among Veterans and aging adults. Her doctoral work and research interests involve the intersection of military-induced auditory injuries within the framework of the larger social context.

**Presentation overview:**
Exposure to hazardous noise levels can result in a host of auditory problems including hearing loss, tinnitus, and decreased sound tolerance. When tinnitus and hearing problems occur in the absence of audiometric hearing loss, it is important to explore other variables that could mediate the relationship between noise exposure and developing these auditory-related phenomena. Epidemiologic approaches offer a unique means to explore the natural history and impact of tinnitus and other auditory disorders at a population level. This presentation will review the steps involved to examine these relationships using a priori causal models. Conceptual models are used in epidemiologic research to guide statistical analyses and elucidate the complex relationships between exposures like noise and outcomes such as tinnitus. Specifically, data from longitudinal studies can be used to answer questions pertaining to etiology, prevalence, and effects of auditory-related conditions in specific populations (e.g., Veterans).

**Funding support:** This work was supported by a Department of Defense Congressionally Directed Medical Research Program Investigator-Initiated Research Award #PR121146 and Joint Warfighter Medical Research Program Award #JW160036. This material is the result of work supported with resources and the use of facilities at the VA RR&D NCRAR (Center Award #C9230C) at the VA Portland Health Care System in Portland, Oregon.
Ototoxicity of Aminoglycosides in Patients with Cystic Fibrosis
Angela Garinis, PhD and Lisa Hunter, PhD
Thursday, 1:15 – 2:05pm

About Dr. Garinis:
Angela Garinis, Ph.D., is an clinical audiologist at OHSU and the VA Portland Health Care System, Assistant Professor in the Oregon Hearing Research Center (OHRC) at OHSU, and a Research Investigator at the VA NCRAR. Dr. Garinis’ research program investigates the middle ear and cochlear mechanisms of auditory perception in patients with cystic fibrosis (CF). She is particularly interested in understanding the clinical risk indicators associated with onset of aminoglycoside-induced hearing loss in this population. Dr. Garinis has extensive experience as an auditory scientist using both behavioral and physiologic tests of hearing to better understand the mechanisms of ototoxicity in a clinical population. Specifically, Dr. Garinis has NIH-NIDCD funding to investigate the effects of ototoxic treatments on the cochlear and medial efferent auditory system in persons with CF treated with aminoglycosides.

About Dr. Hunter:
Lisa Hunter, Ph.D., is the Scientific Director for Audiology in the Communication Sciences Research Center at Cincinnati Children’s Hospital Medical Center, and a Professor of Otolaryngology and Communication Sciences and Disorders at the University of Cincinnati. Dr. Hunter has 30 years of clinical, research and teaching experience focusing on the pediatric population. She is a graduate of the University of Cincinnati and the University of Minnesota. Her current areas of research are in advanced physiologic tools for assessment of ototoxicity, and detection of hearing loss in newborns. She serves on the board of the American Auditory Society.

Presentation overview:
Aminoglycoside antibiotics are used world-wide to treat drug-resistant chronic lung infections. These lifesaving drugs unfortunately cause hearing loss due to ototoxicity, the effects of which progress from the base to the apex of the basilar membrane (inner ear). Therefore, in order to detect ototoxicity sooner, the higher frequency region is important to assess. This talk will provide an overview of cystic fibrosis (CF) and the latest research on aminoglycoside-induced ototoxicity in this patient population. Research-evidence will be presented regarding the effects of cumulative intravenous aminoglycosides dosing on the hearing of teen and adult patients with CF. This presentation will also review novel data using both extended high-frequency pure-tone audiometry, transient-evoked otoacoustic emissions to chirps (TEOAEs), and speech-in-noise thresholds (BKB-SIN) to detect ototoxicity in pediatric patients with CF treated with aminoglycosides, compared to age-matched untreated controls. Longitudinal data and case studies will be discussed.

Funding support: Funding provided by NIH-NIDCD (#DC010202, PIs: Keefe, Feeney & Hunter; #DC016128, PI: Garinis; Cincinnati Clinical Translational Research Center Award #R01DC014078, PI: Moore), Decibel Therapeutics (Pis: Hunter & Garinis), NIHNCATS Award (#5UL1TR001425-04) and CCHMC Place Outcomes Research Award (PI: Hunter); CCHMC Research Foundation.
Ototoxicity of Chemotherapeutic Agents
Kristin Knight, M.S. and Dawn Konrad-Martin, PhD
Thursday, 2:05 – 2:55pm

About Ms. Knight:
Kristin Knight, M.S., CCC-A, FAAA, is a pediatric audiologist and Associate Professor in the Department of Pediatrics at Doernbecher Children’s Hospital, Oregon Health and Science University. Her clinical research has focused on pediatric ototoxicity monitoring and identifying treatment- and patient-related risk factors for platinum-induced hearing loss. She has been a member of the Children’s Oncology Group Auditory Late Effects Committee since 2008 and she is the study audiologist for two Children’s Oncology Group pediatric clinical trials.

About Dr. Konrad-Martin:
Dawn Konrad-Martin, Ph.D., is the Associate Director of the National Center for Rehabilitative Auditory Research (NCRAR) at the VA Portland Health Care System, and an Associate Professor of Otolaryngology and Head and Neck Surgery at the Oregon Health & Science University (OHSU). The last 16 years of Dr. Konrad-Martin’s research funded by VA RR&D Service has added to the knowledge base, clinical tools and technology available to address the problem of ototoxicity. During this period, Dr. Konrad-Martin and her collaborators have developed methods to accomplish time-efficient ototoxicity screening on the oncology unit. This includes: the use of insert and circumaural earphones for “chair-side” testing outside the sound booth, condensed behavioral and physiological (otoacoustic emission) screening approaches, pre-exposure ototoxicity risk assessments and development of a device for portable automated testing and tele-health. She has been a member of the American Speech Language and Hearing Association Scientific Affairs Committee, the Department of Defense Hearing Center of Excellence, Pharmaceutical Interventions for Hearing Loss working group, and is a member of the advisory board for the Translational Hearing Center in the Department of Biomedical Sciences at Creighton University.

Presentation overview:
Ototoxicity from platinum-based chemotherapy is a frequent cause of acquired, progressive sensorineural hearing loss (SNHL) among cancer survivors. Approximately 14 million people in the US have cancer, with ~1.6 million new cases diagnosed each year. Within VA last year alone, an estimated 10,421 patients received chemotherapy with cisplatin, carboplatin or oxaliplatin. Forty to 80% of patients treated with cisplatin or carboplatin demonstrate ototoxic SNHL and/or tinnitus, leaving a significant fraction of patients who retain their pre-treatment auditory function despite high cumulative drug dosing. Oxaliplatin is less ototoxic overall yet can cause severe ototoxicity in some patients. Because of uncertain susceptibility, early clinical indicators of ototoxicity can allow optimal (and earlier) allocation of ototoxicity monitoring (OM) and aural rehabilitation resources and, when medically appropriate, consideration of a less toxic treatment. While OM is standard of care for children treated with cisplatin, OM often fails to take place for adult cancer patients both within and outside VA. This presentation will discuss the risks and clinical presentation of ototoxicity from platinum-based chemotherapy among in children and adults. Options for monitoring hearing in infants and young children will be presented, as well as development of time efficient methods to identify ototoxicity in adults that can be implemented outside of the sound booth on the oncology unit. Cross-disciplinary consensus is needed to inform OM outcome reporting, determination of actionable ototoxic changes and evaluation schedules. Optimizing hearing outcomes for patients battling cancer is crucial to maintain quality of life because hearing loss impedes communication, psychosocial adjustment, and enjoyment of life activities.

Funding support: Ms. Knight’s research is supported in part by NIH NINDS: 5 R01 NS033618; PI: Edward Neuwelt, M.D.; Dr. Konrad-Martin’s research is supported in part by VA RR&D (Merit Award C0239R; Center Award #C9230C).
Military ototoxic solvent exposures and the interaction with noise exposure

William Murphy, PhD
Thursday, 3:30 – 4:20pm

About Dr. Murphy:

William J. Murphy, Ph.D., is a Captain in the United States Public Health Service Commissioned Corps and is coordinator for the Hearing Loss Prevention cross sector for the National Institute for Occupational Safety and Health. He is an active member of the National Hearing Conservation Association and a Fellow of the Acoustical Society of America (ASA). He is currently the chair for the ASA’s American National Standards Institute (ANSI) Accredited Standards Committee S3 for Bioacoustics. He has provided leadership to the ASA as chair of the Technical Committee on Noise and through work with the national and international standards on noise.

Presentation overview:

Although noise is the predominant source of work-related hearing loss, evidence has demonstrated that chemical toxicants can also cause hearing loss and enhance sensitivity to noise. Types of chemicals that have been studied for their ototoxicity include: solvents, metals, asphyxiants, carbon monoxide, organotins, PBCs, and pesticides. Hearing may be affected by high concentrations of chemicals even in the absence of noise. Reports from animal experiments confirm earlier observations that chemicals can interact synergistically with noise or potentiate noise effects on the auditory system. The interaction is modified by several exposure specific parameters, including the temporal distribution of the noise exposure. Existing evidence has prompted the proposal of new guidelines and standards on hearing loss prevention in the US and abroad. A new concept of creating an ototoxicity notation has been proposed. Impulsive noise presents a significant hazard to hearing in the military environment. Mitigation of risk through noise control engineering solutions in combination with personal protective equipment is important to maintaining healthy ears in the military. This presentation will examine the recent developments and discuss alternative strategies for preventing auditory effects of exposure to ototoxic chemicals and impulsive noise.

Funding support: The work was supported by NIOSH intramural funds.

Patient Perspectives Presentations

Thursday, 4:20 – 5:00pm

Videotaped and interactive patient testimonials

This session presents videotaped and interactive patient testimonials to share the patient’s perspective on key issues related to the burden of auditory disorders resulting from exposure to ototoxic medications or noise as well as the importance of quality of life and optimizing functional ability. The overall hypothesis of this conference is that clinicians and researchers will be able to devise improved rehabilitative and pharmaceutical interventions if they can be shaped according to the specific auditory deficits, sites of lesion, and the priorities of individual patients. After attending this session, attendees will be able to discuss how to optimize their patient care or research strategies by supporting the patient’s functional abilities, goals for communication and coping in daily life, including helping them maintain support through interpersonal, social and community interactions in ways that are meaningful to them. Objectives of this session are to help the attendee consider more than the physical symptoms of hearing loss and tinnitus, to take into account the whole person, including psychological, social and cultural factors as well as overall health status. Through these personal stories, attendees will also learn that important healing may be achieved by educating and advocating, working collaboratively with the individual, supportive family members and with fellow professionals.
Regeneration of hair cells, synapses, and neurons
Albert Edge, PhD
Thursday, 8:00 – 8:50am

About Dr. Edge:
Albert Edge, Ph.D., is Eaton Peabody Professor in the Department of Otolaryngology at Harvard Medical School and Director of the Tillotson Laboratory for Cell Biology of the Inner Ear at Massachusetts Eye and Ear. He was a Postdoctoral Fellow in the Department of Biological Chemistry at Harvard Medical School where he was an Iacocca Fellow and a Capps Scholar. His research is focused on mechanisms of stem cell differentiation and cellular repair in the cochlea. He has discovered cochlear progenitor cells that express Lgr5, a gene also expressed in the stem cells of the intestine. The long-term objective of the lab is to regenerate sensory hair cells and their synapses with neurons.

Presentation overview:
The cochlea has a limited ability to replace damaged cells, but some cells isolated from the cochlea have properties of progenitor cells. We have identified Lgr5, a downstream target of the Wnt pathway and a protein found in intestinal epithelial stem cells, as a marker for supporting cells that can act as hair cell progenitors in the mammalian cochlea. Hair cells regenerate spontaneously in neonatal mouse ears following ototoxic damage and the new hair cells arise mostly from Lgr5-expressing cells. Differentiation of new hair cells after damage is dependent upon spontaneous activation of the Wnt pathway and can be further stimulated by inhibition of Notch signaling. Neurons can also be grown from embryonic stem cells and these neurons, when added to in vivo organ of Corti cultures, grow new fibers that contact hair cells and form synapses. Formation of synapses requires the addition of neurotrophins. Further enhancement in growth and synapse formation could be achieved by overcoming inhibition imposed by molecules in the organ of Corti that blocked the formation of synapses between neurons and hair cells. Inhibition of the axonal guidance molecule RGMa increases synapse formation, as documented by detection of pre- and postsynaptic specializations in close apposition. New synapses were identified by staining of C-terminal binding protein (CTBP2) at the presynaptic (hair cell) side and postsynaptic density 95 (PSD95) at the postsynaptic (neuron) side. Methods for the replacement of neurons and their synapses with hair cells could lead to restoration of cochlear function after noise damage to the organ of Corti.

Funding support: NIH DC007174 and DC014089.

Preventing Ototoxicity with Otoprotectants
Jian Zuo, PhD
Friday, 8:50 – 9:40am

About Dr. Zuo:
Jian Zuo, Ph.D., obtained his B.S. in Biomedical Engineering in Huazhong University of Science and Technology in Wuhan, China in 1985. He then obtained his PhD in Physiology from UCSF in 1993. After postdoc training in Rockefeller University, he became faculty at St. Jude Children’s Research Hospital in Memphis in 1998, where he remained for ~20 years. He recently moved to Creighton University School of Medicine as the Chairman and Professor in the Dept. of Biomedical Sciences in April 2018. His research interests include neurodegeneration and function, regeneration, and protection of sensory hair cells in the cochlea.
Presentation overview:
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. This talk will describe the process of identifying, developing, and testing otoprotectant drugs for preventing ototoxicity. First, unbiased high-throughput screens for small molecules that prevent cisplatin-induced hearing loss in a cochlear derived cell line were performed. The hit compounds were further validated in cochlear explants, zebrafish lateral-line neuromasts in vivo, and eventually in mouse and rat cochleae in vivo. This resulted in identification and characterization of multiple potent compounds that exhibit protection against not only cisplatin, but also antibiotics and noise-induced hearing loss. Several targets of top compounds were further investigated in knockout mouse models. Medicinal chemistry efforts led to a new generation of otoprotectants. To treat hearing loss, genetic mouse models were developed in which hair cell regeneration occurred at adult ages. Based on these genetic manipulations, high-throughput screens of small molecules that mimic the genetic models were performed. When delivered transtympanically in adult mice, the top compounds can induce regeneration of immature hair cells. Combinatory applications of these compounds could provide therapeutic intervention of hearing loss in clinic.

Funding support: NIHR01DC015010, NIHR01DC015444, ONR(N00014-16-1-231), USAMRMC (RH170030), Nebraska State (LB692).

Using Computational Models for Differential Diagnoses of Sensory vs. Neural Damage
Sarah Verhulst, PhD
Friday, 10:10 – 11:00am

About Dr. Verhulst:
Sarah Verhulst, Ph.D., is Associate Professor in Hearing Technology at Ghent University in Belgium. She has a background in electrical and acoustical engineering and received her Ph.D. from the Technical University of Denmark in the topic of cochlear mechanics and otoacoustic emissions. After post-doctoral training at Boston and Harvard University incomputational auditory neuroscience and an Assistant Professorship at Oldenburg University, she joined Ghent University in 2016. She uses an interdisciplinary approach (modeling, physiology, machine-learning, perception) to study how hearing impairment affects sound encoding.

Presentation overview:
While we have known for 10 years that sensorineural hearing loss also comprises age- or noise-induced synaptic auditory-nerve fiber damage (cochlear synaptopathy), we still lack sensitive diagnostic methods that quantify this damage non-invasively and differentially in humans. This talk will explain how advanced computational models of the human (hearing-impaired) auditory periphery can be used to develop acoustic stimuli for non-invasive auditory EEG tests (akin to ABR, ASSR testing protocols), which can quantify the individual degree of synaptopathy in the presence of potentially co-existing outer hair cell damage. Where state-of-the-art ABR or ASSR methods have difficulty relating response amplitudes to the details of the underlying sensory or synaptopathy pathology, models can help establish this relationship and ultimately yield a frequency-specific quantification of either aspect of sensorineural hearing loss. This diagnostic detail is important when deciding the most suitable hearing loss treatment strategy or hearing aid algorithm. For example, it is possible to integrate individual patterns of outer hair cell loss and synaptopathy into individualized models of sound processing to develop hearing aid algorithms tailored to each individual. To this end, numerical machine-learning or error-minimization methods can be employed to bring listeners within their optimal hearing range. Numerically-based hearing restoration strategies may end up performing better than conventional amplification algorithms in terms of restoring speech intelligibility.

Funding support: European Research Council (ERC) under the Horizon 2020 Research and Innovation Program (grant agreement No 678120)
Panel Discussion on interdisciplinary, inter-agency perspectives on patient management
Friday, 11:00am – 12:30pm

The goal of this session is to provide an opportunity for attendees to collaboratively discuss strategies for optimizing hearing health and rehabilitation outcomes in individuals at risk for ototoxic or noise-related auditory dysfunction, with input from an array of stakeholders.

About Dr. Al-Malky:
Dr. Ghada Al-Malky, PhD is Director of Education, Senior Lecturer at University College London. Dr. Al-Malky’s research interests include: Bridging the gap between laboratory auditory biophysics and genetics research and clinical applications in human patients; and verifying the clinical usefulness of the continuous advances in auditory rehabilitation as well as establishing how they could be best utilized to improve patients’ quality of life. Her current research is related to investigating the auditory effects of aminoglycoside ototoxicity; assessing incidence, identifying the most appropriate test battery to effectively record their effect on the auditory system, modifying and developing testing instrumentation to allow for early detection of minimal changes in the ear and identifying genetic markers that make certain individuals more susceptible to the ototoxic effect of aminoglycoside antibiotics more than others. This research is aiming to help us better understand this topic and allow for the translation of lab-based research into the clinic setting.

About Colonel Henry:
Colonel LaKeisha Henry, M.D., United States Air Force, serves as Division Chief, Department of Defense Hearing Center of Excellence (HCE), Defense Health Agency, a collaborative effort with the Department of Veterans Affairs. Stationed at Joint Base San Antonio-Lackland, Texas, she leads the HCE as it executes the Congressionally-directed mission to optimize operational effectiveness, heighten medical readiness, and enhance quality of life for Service members and Veterans through collaborative leadership and advocacy for hearing and balanced health initiatives. She recently served as the Otolaryngology Consultant to the Air Force Surgeon General.

About Dr. Hullar:
Dr. Hullar is Professor of Otolaryngology – Head and Neck Surgery, Division of Otology/Neurotology/Skull Base Surgery, School of Medicine at the Oregon Health & Science University, Portland, Oregon. Dr. Hullar’s research interests include outcomes from cochlear implantation, basic and applied science of the vestibular system, and comparative anatomy of the mammalian labyrinth. He has a history of research funding from industry, private foundations, and the NIH. He is associate editor of Ear and Hearing and serves on the editorial board of Otology and Neurotology and Trends in Hearing.

About Dr. Landier:
Wendy Landier, Ph.D., R.N., is an Associate Professor in the Division of Pediatric Hematology/Oncology and Deputy Director of the Institute for Cancer Outcomes and Survivorship in the School of Medicine, University of Alabama at Birmingham. She earned her master’s degree at UCLA and Ph.D. from the University of Hawaii. Her research focuses on understanding and improving health outcomes in childhood cancer survivors, with an emphasis on development, implementation, and refinement of guidelines for survivorship care, ototoxicity, acquisition of health knowledge, and secondary cancer prevention. She is a pediatric nurse practitioner with a clinical focus on the care of childhood cancer survivors. She was integrally involved in the development of the Children’s Oncology Group Long-Term Follow-Up Guidelines and continues to provide oversight over guideline refinement through her role on the Core Guidelines Committee. She also recently co-led the Ototoxicity Working Group for the International Guideline Harmonization Group.
About Dr. Murphy:
William J. Murphy, Ph.D., is a Captain in the United States Public Health Service Commissioned Corps and is coordinator for the Hearing Loss Prevention cross sector for the National Institute for Occupational Safety and Health. He is an active member of the National Hearing Conservation Association and a Fellow of the Acoustical Society of America (ASA). He is currently the chair for the ASA’s American National Standards Institute (ANSI) Accredited Standards Committee S3 for Bioacoustics. He has provided leadership to the ASA as chair of the Technical Committee on Noise and through work with the national and international standards on noise.

About Dr. Ortiz:
Candice “Evie” Ortiz, Au.D., earned her Doctorate in Audiology from the University of South Florida. She is currently a clinical audiologist at Walter Reed National Military Medical Center in Bethesda, MD where she is a subject matter expert in ototoxic monitoring and tinnitus management. Her clinical and research interests are focused in the areas of ototoxicity, tinnitus, and management of treatment-resistant auditory hallucinations. As an advocate for pediatric and adult ototoxic monitoring, Dr. Ortiz is a member of multiple working groups, advisory committees, and multidisciplinary care teams. Dr. Ortiz is currently partnering with scientists and clinicians to develop methods to detect early changes in hearing as a result of ototoxic exposures. Her ultimate goal is to develop a multidisciplinary standard of care approach for the effective monitoring and treatment of ototoxicity.

About Dr. Rubenstein:
Ronald C. Rubenstein, MD, PhD is a Professor of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania (Penn) and Director of the Cystic Fibrosis Center at the Children’s Hospital of Philadelphia (CHOP) and Penn. He is currently a Member of the Cystic Fibrosis Foundation (CFF) Medical Advisory Council and Chair of the CFF Clinical Research Committee, serving in this role since 2003. Dr. Rubenstein’s research interests focus on novel therapeutic strategies for Cystic Fibrosis, with a central hypothesis that drugs or small molecules can affect repair of function of mutant CFTR proteins. Dr. Rubenstein’s work with one such agent, Sodium 4-Phenylbutyrate, provided a critical proof of concept that served as a foundation for the development of now approved modulator agents such as Orkambi and Symdeko. His laboratory’s research into the mechanisms by which the biogenesis of CFTR and other epithelial ion channels relevant to CF are regulated is presently supported by grants from the National Institutes of Health and the CF Foundation. Dr. Rubenstein is also very active in clinical trials that aim to translate this approach to CF therapeutics into useful therapies, as well as in research that aims to understand the mechanisms underlying the development of CF-related diabetes and the risk factors for aminoglycoside-induced hearing loss in CF. Through this work, Dr. Rubenstein is both an advocate for people with CF, and a mentor and teacher for dozens of trainees and junior faculty as they develop their careers.
Breakout sessions: Practical implementation issues
LaKeisha Henry, Col., MD, PhD; Kelly Reavis, MPH, Carmen Brewer, PhD, Evie Ortiz, AuD, Wendy Landier, PhD
Friday, 1:00pm – 2:30pm

About Colonel Henry:
Colonel LaKeisha Henry, M.D., United States Air Force, serves as Division Chief, Department of Defense Hearing Center of Excellence (HCE), Defense Health Agency, a collaborative effort with the Department of Veterans Affairs. Stationed at Joint Base San Antonio-Lackland, Texas, she leads the HCE as it executes the Congressionally-directed mission to optimize operational effectiveness, heighten medical readiness, and enhance quality of life for Service members and Veterans through collaborative leadership and advocacy for hearing and balanced health initiatives. She recently served as the Otolaryngology Consultant to the Air Force Surgeon General.

About Ms. Reavis:
Kelly M. Reavis, MS, MPH, is a Research Audiologist at the U.S. Department of Veterans Affairs, Rehabilitation Research and Development, National Center for Rehabilitative Auditory Research, located at the VA Portland Health Care System. She is also a PhD candidate in the Epidemiology program at Oregon Health & Science University-Portland State University School of Public Health. Her research interests are centered on the transfer of evidence-based protocols for the detection of hearing loss and tinnitus secondary to chemotherapeutic exposures from the laboratory to the clinic. Additionally, she is interested in identifying risk factors for, and the distribution of, auditory injuries among Veterans and aging adults. Her doctoral work and research interests involve the intersection of military-induced auditory injuries within the framework of the larger social context.

Presentation overview:
Building clinical databases at the VA and DoD to improve patient hearing healthcare and optimize research

Recently, the Department of Defense (DoD) and the Department of Veterans Affairs (DVA) has put efforts toward the exchange of hearing health care information with the goal of improving the quality and cost effectiveness of the care provided by each department to its beneficiaries. This effort, led by the DoD Hearing Center of Excellence, has resulted in a unique auditory injury registry populated with hearing health care data from both the Military Health System and the Veterans Health Administration, known as the Joint Hearing and Auditory System Injury Registry (JHASIR). In addition to providing audiologists and other hearing healthcare practitioners with quick and efficient access to the complete audiological picture of each member of the Armed Forces and our nation’s Veterans, the registry also encourages and facilitates the conduct of research, the development of best practices, and clinical education. This breakout session will discuss the background and building of this unique audiological database at the DoD to improve patient care and research. It will include a demonstration of the JHASIR to expand awareness and present a pathway for research access. Discussion will include highlights of, as well as a deeper dive into, some of the administrative data sources contributing to JHASIR. Further discussion will follow around the opportunities and limitations of using administrative data, collected originally for the purposes for diagnosis and treatment, for research.
Presenters:  Candice Ortiz, AuD, Wendy Landier, PhD, Carmen Brewer, PhD

About Dr. Ortiz:
Candice “Evie” Ortiz, Au.D., earned her Doctorate in Audiology from the University of South Florida. She is currently a clinical audiologist at Walter Reed National Military Medical Center in Bethesda, MD where she is a subject matter expert in ototoxic monitoring and tinnitus management. Her clinical and research interests are focused in the areas of ototoxicity, tinnitus, and management of treatment-resistant auditory hallucinations. As an advocate for pediatric and adult ototoxic monitoring, Dr. Ortiz is a member of multiple working groups, advisory committees, and multidisciplinary care teams. Dr. Ortiz is currently partnering with scientists and clinicians to develop methods to detect early changes in hearing as a result of ototoxic exposures. Her ultimate goal is to develop a multidisciplinary standard of care approach for the effective monitoring and treatment of ototoxicity.

About Dr. Landier:
Wendy Landier, Ph.D., R.N., is an Associate Professor in the Division of Pediatric Hematology/Oncology and Deputy Director of the Institute for Cancer Outcomes and Survivorship in the School of Medicine, University of Alabama at Birmingham. She earned her Master’s Degree at UCLA and Ph.D. from the University of Hawaii. Her research focuses on understanding and improving health outcomes in childhood cancer survivors, with an emphasis on development, implementation, and refinement of guidelines for survivorship care, ototoxicity, acquisition of health knowledge, and secondary cancer prevention. She is a pediatric nurse practitioner with a clinical focus on the care of childhood cancer survivors. She was integrally involved in the development of the Children’s Oncology Group Long-Term Follow-Up Guidelines and continues to provide oversight over guideline refinement through her role on the Core Guidelines Committee. She also recently co-led the Ototoxicity Working Group for the International Guideline Harmonization Group.

About Dr. Brewer:
Carmen Brewer, Ph.D. is Chief of the Audiology Unit within the Division of Intramural Research at the National Institute on Deafness and Other Communication Disorders at the NIH where she has worked for 17 years. Her research interests include deep phenotyping of auditory and vestibular function in persons with rare diseases and evaluation of ototoxic effects of treatments undergoing clinical trial as well as known ototoxic agents.

Presentation overview:

Otitotoxicity management: Practical considerations for clinical application

This interactive session will focus on clinical and practical considerations for a successful ototoxicity management program. Discussion will include program development and implementation, logistical barriers, factors critical to program success, and the importance of communication with care providers and patients. Topics will be led by an oncology nurse practitioner and two audiologists with clinical experience in these areas. The session will include presenter-led discussion with opportunities for audience input and questions.
1. **Alternation of synaptic ribbon distribution after a single-dose ototoxic injury**

*Hongzhe Li, PhD*¹,², *Liana Sargsyan, MD*¹, *Alisa Hetrick, MS*¹, *Glen Martin, PhD*¹,²

¹Research Service, VA Loma Linda Healthcare System, CA 92350, USA
²Department of Otolaryngology - Head & Neck Surgery, Loma Linda University School of Medicine, Loma Linda, CA 92357, USA

**Introduction:** Ribbon-synaptic pathologies have been reported after multiday injections of aminoglycosides. The pathologies, at carefully titrated doses, could occur without overt hair cell damage, thus, mimicking the condition of hidden hearing loss that is induced by moderate noise exposure. Here, we examined the corresponding synaptic effect of a single gentamicin injection in combination with a loop diuretic.

**Methods and Materials:** A single fixed dose of gentamicin (200 mg/kg body weight) was injected intraperitoneally (i.p.) into adult C57BL/6 mice, followed 30-min later by various doses of furosemide (50, 100, or 400 mg/kg). Alternatively, mice received various doses of gentamicin (25, 50, 100, 200, or 400 mg/kg) followed by a fixed dose of furosemide (200 mg/kg). Distortion product otoacoustic emissions (DPOAEs) and auditory brainstem responses (ABRs) were measured 3- and 7-day posttreatment. Seven days after treatment, cochleae were micro-dissected, immunolabelled and imaged by confocal microscopy at the 8-, 12- and 16-kHz frequency locations.

**Results:** For the fixed doses of gentamicin groups, ABR thresholds and DPOAEs were unaltered posttreatment, especially, with lower doses of furosemide. Morphologically, no hair-cell loss was observed, but the number of synaptic ribbons slightly increased, when examined at the 12-kHz location. With the highest dose of furosemide (400 mg/kg), ABR thresholds were elevated and DPOAEs reduced at 3-day posttreatment, and this change was maintained when measured at 7-day posttreatment. In addition, the ribbon numbers were reduced. For all the fixed-dose furosemide groups, ribbon numbers were not altered at any of the examined locations. Confocal-image analysis indicated a movement of synaptic ribbons towards the pillar side of inner hair cells after gentamicin and the higher doses of furosemide at the 12-kHz location.

**Conclusion:** Single gentamicin injections in combination with furosemide-induced ribbon synaptic pathologies include an alteration of ribbon distribution, primarily manifested by a shift towards both the pillar and cuticular sides of hair cells. The number of synaptic ribbons did not decrease unless a certain degree of hair-cell damage was observed.

**Funding support:** This work was supported in part by DoD W81XWH-14-1-0006 to HL.

2. **Relationship Between Noise Exposure and Auditory Complaints in Service Members and Veterans with Normal Hearing**

*Leslie D. Grush AuD*¹, *Sarah M. Theodoroff, PhD*¹,², *Kelly M. Reavis, MS, MPH*¹,³, *Emily J. Thielman, MS*¹, *James A. Henry, PhD*¹,²

¹VA RR&D National Center for Rehabilitative Auditory Research (NCRAR), Veterans Affairs Portland Health Care System, Portland, OR
²Oregon Health & Science University, Department of Otolaryngology/Head & Neck Surgery, Portland, OR
³Oregon Health & Science University, School of Public Health, Portland, OR

Exposure to hazardous noise levels can result in hearing loss and self-perceived hearing difficulties such as difficulty understanding speech. When hearing difficulties occur in the absence of conventional audiometric hearing loss, it is important to explore other variables that could mediate the relationship between noise exposure and the auditory complaints. It has been theorized a possible mediating pathway between noise exposure and auditory complaints includes subclinical cochlear pathophysiology.

To explore this theory, we will examine the strength of associations between noise exposure and distortion product otoacoustic emissions (DPOAE) in individuals with audiometric hearing thresholds ≤ 20 dB HL 25-8 kHz. We hypothesize that in these normal hearing participants, higher degree of noise exposure will be associated with increased reporting of hearing difficulties and abnormal DPOAEs.
Baseline data will be analyzed from 690 individuals (286 Service members; 404 Veterans) participating in the “Noise Outcomes in Servicemembers Epidemiology (NOISE) Study.” Noise exposure will be identified using a comprehensive questionnaire, the Lifetime Exposure to Noise and Solvents Questionnaire. Complaints of hearing difficulties will be identified using a question from the Hearing History Questionnaire: “Have you had any difficulties hearing speech or other sounds?” DPOAEs will be measured using a Mimosa Acoustics, Inc., HearID System. Cross-sectional associations will be examined between noise exposure and outcomes of interest.

This research is taking a systematic approach to evaluate early signs of noise injury. Findings will help Department of Defense and VA audiologists understand how noise exposure associated with military service might increase risk for a range of auditory physiological and perceptual problems that manifest prior to hearing loss being detected using conventional audiometry.

**Funding support:** This work was supported by a Department of Defense Congressionally Directed Medical Research Program Investigator-Initiated Research Award (#PR121146), a Joint Warfighter Medical Research Program Award (#JW160036), and a U.S. Department of Veterans Affairs Rehabilitation Research and Development Service Research Career Scientist Award (#C9247S).

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**3.** Physiological measures of efferent and afferent auditory nerve activity in young Veterans and non-Veterans

Sean Kampel, AuD¹ and Naomi Bramhall, PhD¹

¹VA RR&D National Center for Rehabilitative Auditory Research (NCRAR), Veterans Affairs Portland Health Care System, Portland, OR

The efferent medial olivocochlear (MOC) reflex reduces the gain of the outer hair cell (OHC) cochlear amplifier by modifying OHC motility and basilar membrane motion. This gain reduction is thought to provide protection from loud noise exposure and improve signal detection in noise. Animal models indicate that moderate noise exposure can enhance MOC reflex strength, while higher intensity noise exposure can reduce reflex strength. This may explain why speech perception in noise difficulty is a common complaint even among individuals with normal auditory thresholds. Noise-related damage to the synapses between the inner hair cells and the afferent auditory nerve fibers has also been demonstrated in animal models and is associated with a reduction in the amplitude of wave I of the auditory brainstem response (ABR). Synaptic loss is expected to impact speech-in-noise perception without necessarily affecting auditory thresholds. Although synaptic number cannot be measured in humans during life, we have previously demonstrated reduced ABR wave I amplitudes (WIA) among Veterans with high noise exposure during their military service and non-Veterans with a history of firearm use. However, it is unclear how efferent activity is impacted by noise exposure in humans and how this relates to afferent activity. MOC reflex strength can be estimated by measuring otoacoustic emissions with and without a suppressor presented to the contralateral ear and calculating the level difference between the responses. This study measured contralateral suppression of otoacoustic emissions (CSOAEs) and WIA of the ABR in young Veterans and non-Veterans with normal audiograms. The results indicate an impact of military noise exposure on both CSOAEs and WIA. This suggests that noise exposure can lead to efferent and afferent auditory damage, both of which may contribute to speech perception difficulties. This also has implications for how previous noise exposure may modulate susceptibility to future noise damage.

**Funding support:** This work was funded by: Department of Veterans Affairs, Veterans Health Administration, Rehabilitation Research and Development Service Awards #C2104-W and #C9230-C.

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**4.** Validity of computer-based extended high-frequency audiometry with insert earphones

Dirk Koekemoer, MBChB¹, Hlologelo Ramatsoma, BSc¹, Vera-Genevey Hlayisi, MSc²

¹eMoyo Research Centre, Johannesburg, South Africa
²University of Cape Town, Department of Communication Science and Disorders

**Background:** Literature has established extended high frequency (EHF) audiometry as a feasible and reliable method for the monitoring and early identification of ototoxicity, age-related deterioration, acoustic trauma and noise-induced
hearing loss. The use of insert earphones in conventional audiometry has been validated by numerous clinical studies, however, there is a paucity of studies validating the use of insert earphones as a transducer for EHF audiometry.

**Aims:** The purpose of this study was twofold:

1. to determine the equivalent threshold sound pressure level (ETSPL) values in EHF audiometry for the KUDUwave insert earphones.
2. To validate EHF audiometry using insert earphones with a computer-based audiometer -KUDUwave.

**Method:** A within-subject repeated measures design was utilized for both aims/ phases of this study. Participants: In total, 35 subjects participated in this research study. Twenty-five subjects, aged between 18 and 25 years of age - equally distributed in sex were used for the first part of this study. For the second part, a sample of 10 participants were invited to be part of the study. There were 3 males and 7 females with ages ranging from 23-52 years.

**Results:** Otoscopy and tympanometry testing for all participants indicated normal findings. The current study findings showed that there is no statistical difference between EHF absolute thresholds between the industry standard and the computer-based audiometer recordings (p = 0.95) - using the ETSPL values determined in the first part of the study.

**Conclusion:** Therefore, the findings of the current study indicate that a mobile, computer-based audiometer, is a valid form of assessment of pure tone air conduction of the EHF outside of a sound-booth.

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### Optimizing Auditory Brainstem Response Acquisition using Interleaved Frequencies

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Auditory brainstem responses (ABRs) are an assay used to characterize auditory threshold and neuronal survival in a wide range of disorders affecting hearing sensitivity. The ability to assess both auditory threshold and auditory nerve integrity are critical in studies of ototoxicity and noise-exposure. However, ABR assays are a time-consuming process. Hundreds of averages are required to obtain a measurable waveform and adaptation in the auditory nerve limits the rate at which responses to multiple frequencies and levels can be acquired.

Previous studies developed a rapid acquisition paradigm in which a train of multiple frequencies and levels were interleaved [1]. With careful ordering of the frequencies and levels in the stimulus train, adaptation in the auditory nerve may be minimized while increasing the rate at which tone bursts are presented. We demonstrate that our interleaved stimulus design reduces ABR acquisition time by more than half with minimal effect on thresholds, wave amplitudes, and latencies. A modified application of our interleaved stimulus design permits acquisition of large wave 1 through 5 amplitudes with no effect on ABR thresholds or acquisition times compared to data obtained with conventional stimuli.

In summary, the interleaved approach significantly benefits any study that requires rapid assessment of auditory function. The interleaved stimulus design strategy reduces the acquisition time to acquire ABR thresholds permitting assessment of a larger set of frequencies or subjects per unit time than conventional ABR design approaches.


**Funding support:** NIDCD R21DC016969, Hearing Health Foundation Emerging Research Grant.
Given the intense sound levels and pressure waves associated with blast exposures, it comes as no surprise that many Veterans returning from recent conflicts report struggling with hearing difficulties and tinnitus. While several studies have evaluated the impact of noise exposure on subjective reports of hearing ability and tinnitus, despite the presence of normal audiometric thresholds, very few have examined the role of post-traumatic stress disorder (PTSD).

Data, from 68 Veterans, evaluating the effects of PTSD and mild traumatic brain injury from blast exposure (mTBI) on tinnitus prevalence and tinnitus severity were presented at the NCRAR conference in 2017. Here we provide an updated look at those findings in over 175 participants. In addition, we investigate the impact of PTSD on self-reported hearing ability.

All participants were Veterans or service members between the ages of 20-50 with normal or near normal standard audiometric thresholds (.25-8kHz). Participants were placed into one of four groups: control, mTBI-only, PTSD-only, or mTBI+PTSD. Presence of tinnitus was determined through self-report, while tinnitus severity was evaluated using the Tinnitus Functional Index (TFI; Meikle et al., 2012). Self-report of hearing ability was assessed using the Hearing Handicap for Adults (HHIA; Newman et al., 1990) and the Speech, Spatial and Qualities of Hearing Scale (SSQ; Gatehouse & Noble, 2004).

This larger sample supports the previous finding of a superposition effect for PTSD and mTBI for tinnitus severity and extends it to other aspects of hearing ability.

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Scholarship recipient

Predictors of Complex Speech Perception in Veterans and Non-Veterans with Normal Hearing

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In the general population, an estimated 12% of individuals with normal auditory thresholds report hearing difficulty. Complaints speech perception difficulty in the context of a normal audiogram are even more prevalent among military Veterans, likely as a consequence of noise exposure. Recent studies have focused on the impact of noise-induced cochlear synaptic loss (as indicated by the amplitude of wave I of the auditory brainstem response (ABR)) on complex speech perception in individuals with normal audiograms, without finding a clear relationship. However, other factors, such as subclinical outer hair cell (OHC) damage and cognitive ability may also affect speech perception. For example, deficits in aspects of cognition such as working memory and attention are associated with poorer speech in noise perception. Anxiety disorders such as PTSD, common in the Veteran population, that reduce overall working memory and attention capacity might be expected to impair complex speech perception. This study investigated the impact of
OHC function (measured with distortion product otoacoustic emissions (DPOAEs)), synaptic/neural function (measured by ABR wave I amplitude), and cognitive function (measured by self-report of a PTSD diagnosis and the Letter Number Sequencing test) on a variety of measures of complex speech perception in two samples of young Veterans and non-Veterans with clinically normal auditory thresholds. Study findings show important cognitive effects on all speech perception outcomes examined, including self-report. Specifically, PTSD and working memory ability were predictive of many of the speech perception outcomes. In addition, the results demonstrate that OHC function and neural/synaptic loss have limited predictive value for complex speech perception in these samples. This does not necessarily mean OHC and synaptic damage do not impact complex speech perception. Rather, these findings may reflect the limited OHC dysfunction in these samples and/or the degree of measurement error associated with ABR wave I amplitude.

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### Scholarship recipient

**8.**

**Wideband acoustic reflex growth in aminoglycoside-exposed cystic fibrosis patients**

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Individuals with cystic fibrosis (CF) often experience multiple pulmonary exacerbations which are frequently treated with intravenous (IV) aminoglycoside (AG) antibiotics. This class of antibiotics, such as tobramycin and gentamicin, have known ototoxic effects shown in both preclinical and human data. Preclinical animal data suggest that in addition to damaging cochlear hair cells, AGs may cause damage to neural mechanisms in higher auditory brainstem structures resulting in synaptopathy, with neuronal loss present before a measurable decline in behavioral hearing thresholds. The acoustic reflex growth function (ARGF) has been proposed as a non-invasive, objective measure of cochlear synaptopathy. In both rodent and preliminary human studies, a shallow ARGF has been associated with synaptopathy after noise exposure. However, there is a lack of research on this effect in subjects with exposure to ototoxic drugs. For this study, normal-hearing participants with CF were grouped by lifetime IV AG exposure and compared to an age- and sex-matched group of normal-hearing controls without CF. We examined the wideband ARGF between groups and found a trend of enhanced growth in the group with greatest lifetime IV AG exposure relative to all other groups. These results diverge from the pattern of ARGF observed in studies of noise-induced synaptopathy and suggest a different mechanism of auditory dysfunction for ototoxicity.

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Is a normal audiogram really normal? Measures of auditory sensitivity in a sample of young Veterans and non-Veterans
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Hearing related complaints, such as the perception of tinnitus or difficulty understanding speech in background noise are remarkably common among military Veterans, even those with clinically normal audiograms. One possible explanation for these complaints is subclinical outer hair cell dysfunction resulting from military noise exposure. The clinical audiogram is restricted to pure tone thresholds at frequencies from .25-8 kHz. However, pure tone thresholds in the extended high frequencies (9-16 kHz) and distortion product otoacoustic emissions (DPOAEs) may provide additional information about outer hair cell function. In this study, DPOAEs from 1-8 kHz, pure tone thresholds from .25-16 kHz, and self-report of frequent or constant tinnitus were assessed in a sample of 103 young Veterans and non-Veterans with normal audiograms. All non-Veterans had minimal self-reported noise exposure history, including no history of firearm use, and served as a low noise exposure control group. Results indicate that mean air conduction thresholds, both in the standard audiometric range and in the extended high frequencies, are 1-4 dB poorer for Veterans compared to controls. Mean DPOAE levels are also poorer (2-4 dB) across frequency for Veterans compared with non-Veterans. Group differences for both air conduction thresholds and DPOAE levels were similar across frequency rather than showing greater differences in the high frequencies, suggesting that noise-induced cochlear damage in young Veterans tends to be widespread rather than focal. Of note, tinnitus was reported much more frequently by Veterans (44.9%) compared with non-Veterans (8.6%) and was associated with poorer pure tone thresholds and DPOAEs.

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Factors Influencing the Prevalence of Amikacin Ototoxicity
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Amikacin is an aminoglycoside antibiotic essential in the treatment of some nontuberculous mycobacterium infections. Amikacin is cochleotoxic and permanent sensorineural hearing loss may occur secondary to sensory cell damage, beginning in the basal turn of the cochlea. Therefore, hearing loss is usually seen in the high frequencies first and then extends to the lower frequencies with prolonged amikacin exposure. This retrospective study explores the prevalence of amikacin ototoxicity as defined by ASHA and the CTCAE and TUNE grading scales and investigates the influence of other factors including sex, route of administration (intravenous vs inhaled), previous amikacin exposure, and pre-existing hearing loss on the prevalence and amount of ototoxicity. The initial and final audiograms of 167 patients (104 females) aged 5-89 years (M:54, SD:21) with a history of amikacin treatment were reviewed. ASHA criteria identified the most individuals as having ototoxic changes (74%), whereas overall prevalence of ototoxicity was similar between the TUNE and CTCAE grading scales (41% and 47% respectively). CTCAE categorized more individuals as grade 3 (18%) than the TUNE (7%). There were no significant differences in prevalence or severity of ototoxic change between males and females (p>0.05). The amount of ototoxic threshold shift was not influenced by previous IV amikacin exposure nor was there a significant difference in prevalence of ototoxic hearing decline between individuals with and without pre-existing
hearing loss \((p>0.05)\). Route of administration affected the amount of ototoxic change with more decline occurring in those treated with IV versus inhaled amikacin \((p<0.05)\). Additionally, we examine possible associations of ototoxicity with renal function and concurrent medications.

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### 11. Sensitivity of delayed cochlear-microphonic components to acoustic trauma

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The cochlear microphonic (CM) constitutes a vector sum of electrical potentials produced by outer hair cells (OHCs). Thus, the CM may be useful for the diagnosis of OHC impairments, such as those resulting from acoustic trauma. According to the classic theory of CM generation, the potentials measured at the round window are dominated by contributions from sources located at the basal, high-frequency end of the organ of Corti, regardless of stimulus frequency. Consistent with this view, the CM has been shown to have little sensitivity to OHC damage located in the mid and apical turns of the cochlea, which are tuned to lower frequencies. Here, we test the predictions of a new theory of CM generation, where CM at the round window represents a combined response from sources located at the basal end of the cochlea and sources located near the tonotopic place of the evoking stimulus. Because these different CM components arrive at the round window with different delays, they can be separated using time-windowing techniques, as demonstrated previously in normally hearing chinchillas. We further predict that the delayed CM components should be more sensitive than the classic short-latency CM to changes in OHC function at apical cochlear locations. We analyzed CMs measured in chinchillas before and after they were exposed to intense sounds affecting either mid- or basal-cochlear regions. As expected, short-latency CM levels were typically decreased when the cochlear base was damaged but remained largely unaffected when hearing-loss was confined to the mid-frequencies. In contrast, the delayed CM components showed greater sensitivity to changes in cochlear sensitivity at mid-frequencies, as predicted by our model of CM generation. Thus, these results indicate that the poor place-specificity of CM recorded with far-field electrodes can be overcome with signal-processing strategies that allow one to separate CM components of different latencies.

**References:**


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### 12. Noise notch definitions affect detection of preclinical auditory changes at extended high frequencies

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Extended high frequency (EHF) sensitivity (>8 kHz) is often overlooked and underutilized as part of clinical assessment, despite evidence supporting its use to detect early changes in people exposed to excessive sound amplitude, such as musicians. Data from Sensaphonics Hearing Wellness clinical database (spanning nearly thirty years) that included musicians’ history and thresholds from .25-18 kHz was compared in musicians with bilateral audiometric notches (from 3-6 kHz, BNM) to musicians with no notches (NNM) and a group of age-matched non-musicians (CON). To be sure even preclinical degrees of change were considered, a novel notch definition, called here the OSHEA, was employed to identify a group of musicians with decreased sensitivity only in the 3-6 kHz region, with all other thresholds required to be ≤ 25 dB HL. An initial comparison of BNM to NNM age-matched peers yielded significant differences in EHF sensitivity...
(Dunckley, et al., 2018). The current study further validates the O'Shea notch definition’s ability to detect EHF differences across groups, by comparing these results with other widely used notch definitions: Hoffman et al., 2006 (HOFF) and Dobie and Rabinowitz, 2002 (DOBIE). Hoffman et al. (2006) defined an audiometric noise notch as the max threshold from 3-6 kHz exceeding by 15 dB the average of .5, 1, 8 kHz at least 5 dB better than the max at 3-6 kHz. Dobie et al. (2002) defined an audiometric notch index: (mean threshold of 1 and 8 kHz) – (mean threshold 2,3,4 kHz); a notch index greater than 0, may indicate a notch. 1,227 patient files with complete audiometric and history information were examined. OSHEA identified 229, HOFF 109, and DOBIE 219, in the BNM group, respectively. OSHEA identified 675, Hoffman et al. (2006) 219, and Dobie and Rabinowitz (2002) 600, in the NNM group, respectively. A group of non-musicians (no professional music experience) were age-matched to the O'Shea BNM data, and served as the CON for all comparisons.

A locally-weighted polynomial regression (LOESS) was fit to each group’s EHF thresholds. LOESS is a non-parametric method to fit a smoothed curve to a population set (Cleveland 1979, 1994). LOESS fits using a smoothing parameter of 0.3 were applied to valid EHF data; the script delivered 95% confidence interval (CI) limits calculated via bootstrapping for each group. Significant differences at the 95% CI were identified between the BNM and NNM groups using OSHEA and HOFF notch definitions, but not using the DOBIE. Significant differences at the 95% CI were identified between the BNM and CON groups using OSHEA and HOFF notch definitions, but not using the DOBIE.

Significant differences in EHF thresholds for musicians with conventional bilateral audiometric notches compared to those without (musician or non-musician) indicate that damage is not limited to the conventional audiometric range. Differences at EHF are noted even using a conservative notch definition who otherwise have normal hearing. These data support the use of EHF audiometry to detect and monitor peripheral function in high risk groups.

**Funding support: No funding is associated with the project.**

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13. **Noise Outcomes in Servicemembers Epidemiology (NOISE) Study: Findings to Date**

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The Noise Outcomes in Servicemembers Epidemiology (NOISE) Study focuses on noise exposure and any exposure or condition that might be associated with auditory injury. The long-term aim of the study is to estimate and describe the prevalence, etiology, and effects of hearing loss and tinnitus in the military population. This presentation will provide a cross-sectional analysis of baseline data from the first 690 study participants.

Data collection takes place at the NCRAR, Portland, Oregon, and at the Department of Defense Hearing Center of Excellence (HCE), San Antonio, Texas, and includes a comprehensive audiologic evaluation and 15 questionnaires. For participants with tinnitus, three additional questionnaires are administered as well as a tinnitus psychoacoustic evaluation.

Early key findings from the NOISE Study include: (1) 43% of participants with higher noise exposure had self-reported hearing difficulty compared to 17% with lower noise exposure; (2) 61% of participants with higher noise exposure had chronic tinnitus compared to 27% with lower noise exposure; (3) 76% of participants with probable TBI/PTSD had self-reported hearing difficulty compared to 21% without probable TBI/PTSD; (4) 89% of participants with probable TBI/PTSD had chronic tinnitus compared to 39% without probable TBI/PTSD; (5) 52% of participants reporting blast exposure had
self-reported hearing difficulty compared to 29% without blast exposure; (6) 72% of participants reporting blast exposure had chronic tinnitus compared to 43% without blast exposure.

After controlling for potentially confounding variables (demographics and service characteristics), an association was observed between probability of hearing loss, chronic tinnitus, or self-reported hearing difficulty and reported noise exposure, probable TBI/PTSD, or blast exposure. These findings suggest that military experiences and exposures, including noise exposure, probable TBI/PTSD, and blast exposure may drive the development of early-onset hearing loss and tinnitus in active-duty Service members and Veterans.

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14. **Prescription Medication Use and Tinnitus Among U.S. Adults**

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Ninety percent of U.S. adults aged 65 years and older uses at least one prescription medication. No study has described associations between use of prescription medications and tinnitus using nationally-representative data. Using data from the 2011-2012 and 2015-2016 National Health and Nutrition Examination Surveys, we examined cross-sectional correlations between prescription medication use and tinnitus among 9428 U.S. adults aged 20-69 years. Tinnitus was defined as, within the past 12 months, having been bothered by ringing, roaring, or buzzing in the ears that lasts 5 minutes or longer and that participants also describe as a problem. Ringing symptoms limited to those after loud noise exposure were not included in the definition. Number of prescription medications used during the past 1 month was ascertained during in-home interviews. We examined the number of prescription medications by report of tinnitus, and also stratified by gender, self-reported hearing ability, difficulty following conversation, firearm use, occupational noise exposure, and head injury. Specific prescription medications were validated by viewing medication containers. Therapeutic classifications were assigned using the Cerner Multum Lexicon Plus, a database of prescription drugs available in the U.S. We examined therapeutic categories (e.g. analgesics) for prevalence of use by report of tinnitus. The estimated unadjusted prevalence of tinnitus was 10.4% and increased monotonically with greater number of prescription medications. Among several groups with greater prevalence of tinnitus (e.g. those with greater hearing difficulty, difficulty following conversation with background noise, firearm use, and occupational noise exposure), we observed a threshold effect, whereby tinnitus prevalence increased up to and including use of two prescription medications. We found the unadjusted prevalence of use of prescription analgesics, anti-depressants, diuretics and other therapeutic categories among people with tinnitus was over two times that of people without.

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A tale of two susceptibilities: Cisplatin ototoxicity variability in similar patients
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Among the literature, the reported prevalence of cisplatin ototoxicity in adults has varied widely from as low as twenty-two percent to as high as one hundred percent. Cisplatin ototoxicity susceptibility also varies widely, but several risk factors have been identified. In general, patients with pre-treatment hearing loss, elderly patients, patients receiving multiple ototoxic medications, patients who experience noise exposure during and/or after treatment, patients who receive high cumulative doses of cisplatin, and patients with renal insufficiency are more at risk for cisplatin ototoxicity.

The purpose of this project is to present the cases of two patients with similar demographic factors and similar ototoxic risk factors who received the same cisplatin treatment course for the same type of cancer, but experienced very different audiologic outcomes following treatment. Both patients BR and DC are male patients who were diagnosed with p16+ squamous cell carcinoma of the base of tongue with nodal involvement. They both were treated with daily radiation and six doses of weekly cisplatin. Both patients reported some occupational noise exposure, but had normal hearing and no tinnitus prior to the start of treatment. BR is 46 years-old, had stage T2N1M0 disease, and has a distant history of smoking of about 1 pack-year. DC is 48 years-old, had stage T1N3M0 disease, and is a never-smoker. BR received a total of 230 mg/m² of cisplatin chemotherapy in five doses of 40 mg/m² and one dose of 30 mg/m². DC received a total of 240 mg/m² of cisplatin chemotherapy in six doses of 40 mg/m². BR did not experience any CTCAE graded hearing change or tinnitus during or following completion of treatment. DC experienced a bilateral, progressive shift in hearing during treatment resulting in a CTCAE Grade 3 hearing change and intermittent bilateral tinnitus following completion of treatment.

No funding support is associated with the project.

Ototoxicity monitoring at the OSUWMC James Cancer Hospital: Barriers and facilitators
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The objective of this project was to evaluate the ototoxicity monitoring program (OMP) currently in place at the James Cancer Hospital (James) and to determine barriers and facilitators to OMP goals.

Goals for OMPs (delineated by ASHA) include: 1) using a standard definition of an ototoxic hearing shift, 2) conducting pre-treatment counseling regarding potential ototoxic effects, 3) including a baseline evaluation before treatment, 4) performing monitoring evaluations at sufficient intervals to document hearing loss progression, and 5) performing longer term evaluations.

The James OMP has met the first goal for OMPs as one definition of an ototoxic hearing shift is used to detect early ototoxic hearing changes and another definition is used to determine the extent to which potentially handicapping hearing loss has occurred. The James OMP has also met the second goal because if a patient is referred to audiology prior to the start of cisplatin chemotherapy, pre-treatment counseling regarding potential ototoxic effects always takes place. The James OMP has met the third goal for OMPs for some specialties. If a patient was referred to audiology for ototoxicity monitoring, ninety-five percent were seen for a baseline evaluation prior to the start of cisplatin chemotherapy. Depending on what is considered “sufficient intervals”, the James OMP has also met the fourth goal for OMPs. Ninety-six percent of patients participating in the OMP were seen for at least one monitor evaluation during cisplatin chemotherapy treatment. The fifth general goal for OMPs has been the most difficult for the James OMP to meet as only eighty percent of patients have completed long-term follow-up.
Barriers to meeting OMP goals at the James include inconsistent referrals, lack of on-site audiology services, and reduced patient compliance. Facilitators in meeting OMP goals include provider buy-in, on-site audiology services, designated OMP staff, and a standard patient scheduling mechanism.

No funding support is associated with the project.

17. **Interest in Progressive Tinnitus Management among Veteran VA Users with Bothersome Tinnitus: A Qualitative Study**

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**Background:** Tinnitus is the most prevalent service-connected disability among military Veterans. As such, the provision of tinnitus clinical services within the Veterans Health Administration (VA) is a priority. Progressive Tinnitus Management (PTM) effectively reduces Veterans’ tinnitus-related distress; however, relatively few Veterans access this service. We sought to understand factors driving interest in PTM among Veterans who use VA services and experience bothersome tinnitus.

**Methods:** We conducted semi-structured telephone interviews in 2019 with Veterans who were diagnosed with tinnitus and who had participated in a mailed or online tinnitus-related survey in 2018. Veterans were purposively sampled to represent national VA users with bothersome tinnitus, with and without comorbid traumatic brain injury (TBI), and who were or were not interested in receiving PTM services. Interviews were conducted by content experts and lasted approximately 45 minutes. Interview recordings were transcribed by study team members. Qualitative data were analyzed using a grounded theory approach.

**Results:** Among 40 Veterans who participated in interviews (32 men, 8 women), half had comorbid TBI. Participants were relatively evenly distributed across age categories, geographic regions, levels of tinnitus severity, and interest in receiving PTM services. Themes related to Veterans’ interest in PTM included: level of need and priority (i.e., relative to other health issues); perceptions of whether tinnitus coping skills could be helpful; past experiences with VA care, particularly mental healthcare; format of PTM delivery (e.g., individual versus group-based; in-person versus telehealth); and receipt of personal recommendations/testimonials from trusted individuals.

**Conclusions:** Our findings highlight factors that influence Veterans’ need for, and readiness to engage in, clinical services for tinnitus. Personalized or otherwise adaptable approaches to PTM referral, counseling, and delivery may help ensure maximal uptake of this evidence-based service among Veterans in the VA system of care. Ongoing research to test effects of such approaches on PTM outcomes is needed.

**Funding support:** C2216-P (Carlson, Kathleen F), July 1, 2016 – Mar 31, 2019, DVA/RR&D, Chronic Tinnitus among Veterans with and without TBI: Service Needs and Interests.
18. Long Term Ototoxicity Monitoring for Children with Platinum-Based Chemotherapy Veterans
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Platinum-based chemotherapy is a common method used to treat pediatric cancers. Children are at risk for acquiring hearing loss during platinum chemotherapy, with permanent hearing loss occurring in 20-90% of children. Because platinum-induced hearing loss cannot be predicted, hearing must be monitored during treatment. Audiologic monitoring usually ends when treatment is discontinued; however, a few recent studies have indicated that children may be at risk for hearing loss progression, or late-onset hearing loss, years after platinum therapy is completed. The goal of this study is to evaluate the prevalence and severity of delayed-onset and progressive hearing loss in children who were treated with platinum chemotherapy at OHSU, to evaluate the time course of changes in hearing after treatment, and to identify possible risk factors for late-onset and progressive ototoxicity.

The study consisted of a retrospective review of audiologic and medical records collected on 522 pediatric patients who received platinum chemotherapy through OHSU. Baseline testing was completed before initial treatment and follow-up testing occurred in conjunction with further treatments, typically at 1-2 month intervals. At the completion of platinum therapy, semi-annual and annual evaluation was recommended for all children. Data was retrieved and analyzed from subjects who met inclusion criteria for age, chemotherapy treatment, and appropriately timed hearing evaluations.

Of the 522 pediatric patients pulled from the Ototoxicity database, 141 met inclusion criteria for this project. Of those 141 pediatric patients, 50 (35.4%) were identified as having progressive or delayed-onset hearing loss. Risk factors for developing progressive or late-onset hearing loss may include age younger than 9 years at time of treatment, a hearing loss of grade 3 or 4 SIOPs after treatment, a diagnosis of Medulloblastoma/PNET, and cisplatin treatment, especially when combined with cranial radiation. Ultimately, this study highlights the need for audiologic monitoring further than current practices.

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Auditory impairments, particularly those resulting from hazardous occupational noise exposures, are pressing concerns for the US Department of Defense (DoD) and Department of Veterans Affairs. However, to date, no studies have estimated the rate of hearing change that occurs during service or how changes may vary by military occupation. Using a retrospective cohort study design, we linked audiometric data collected from Service members as part of the DoD Hearing Conservation Program (HCP) to demographic and military-service characteristics obtained retrospectively from individuals enrolled in the Noise Outcomes In Servicemembers Epidemiology (NOISE) Study. We examined the association between occupations categorized as having a low, moderate, or high probability of exposure to hazardous noise and pure-tone hearing thresholds (500-6000 Hz) using a hierarchical linear model. The analytic cohort was limited to Service members enlisted after September 2001 (n=245). On average, hearing change ranged between -2.0 and 4.7 dB/year and changes over time varied by service branch, audiometric test frequency, and military occupation.
categorization. Generally, higher test frequencies (3-6 kHz) and military occupations with moderate or high probability of noise exposure generally showed poorer thresholds over time. This demonstrates unique use of DoD HCP data, is the first analysis of hearing-threshold shifts over time using such data and adds to the limited literature on longitudinal changes in hearing.

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### 20. Ototoxicity after in utero Exposure to Antiretrovirals

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Current World Health Organization (WHO) recommendations support the use of highly-active antiretroviral therapy (HAART) to prevent the transmission of human immunodeficiency virus (HIV) from mother to child. Previous WHO recommendations on the use of HAART for pregnant and nursing HIV-positive (HIV+) mothers have been modified because of apparent side effects of treatment in children exposed to these drugs in utero. In addition, some of the recommended antiretroviral drugs are believed to cause mitochondrial dysfunction, which may particularly affect the energy-consumptive cochlea, causing auditory effects in exposed offspring. To explore this potential, pregnant and nursing female mice were exposed once per day to a combination of lamivudine and tenofovir, two antiretroviral drugs currently recommended by the WHO for pregnant and nursing HIV+ mothers. Control female mice received saline on the same daily schedule. After weaning, auditory thresholds were assessed in all offspring via auditory brainstem responses from 4-32 kHz. Results indicated that offspring exposed to the antiretrovirals had higher thresholds than unexposed offspring at all tested frequencies except 24 kHz. These preliminary findings suggest the need for additional exploration of the auditory effects of in utero exposure to antiretroviral drugs. If these findings are representative of human pregnant and breastfeeding mothers with HIV, then the current study suggests that the children of these mothers are at risk for antiretroviral-induced auditory problems.

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