

Introduction

Ototoxicity and Noise Damage: From Preclinical Findings to Audiological Management

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Hearing loss and tinnitus are major health concerns because they affect both independence and quality of life, regardless of age, ethnic, racial, or socioeconomic background. Untreated hearing loss has been associated with diminished interpersonal interactions; increased risk of depression (Armstrong et al., 2020), dementia, and cognitive decline (Dawes et al., 2015; Deal et al., 2017; Gurgel et al., 2014; Jayakody et al., 2018); and limited access to health care due to communication barriers (Chang et al., 2018). Two of the most prevalent preventable causes of hearing loss are exposure to high-intensity noise and ototoxins. The U.S. Centers for Disease Control and Prevention (CDC) recently reported that in the United States, at least 10 million adults under 70 years old (6%)—and possibly up to 40 million—exhibit noise-induced damage based on audiometric findings (CDC, 2017). Similar statistics do not exist for cases of ototoxicity, partly due to a lack of proactive hearing surveillance in clinics that prescribe highly ototoxic treatments (e.g., platinum-based chemotherapeutics or aminoglycosides) and in industrial or military occupational settings in which exposures to ototoxic chemicals are common (e.g., printing, construction, manufacturing, aircraft maintenance). However, we *do* know that 1.7 million Americans will be diagnosed with cancer this year and that ototoxic platinum-based chemotherapy is a mainstay of treatment for many solid tumor types (American Cancer Society, 2016). In

addition, over 70,000 people worldwide (30,000 in the United States) have been diagnosed with cystic fibrosis (CF), which is commonly treated with aminoglycoside antibiotics (e.g., tobramycin) to manage lifelong gram-negative bacterial infections (Cystic Fibrosis Foundation, 2020). Over 1,000 new cases of CF are diagnosed per year, and life expectancy continues to improve, which will likely result in an increase of cumulative aminoglycoside dose exposure and ototoxicity risk (Garinis et al., 2017). Oncology and patients with CF, as well as other infectious disease populations, will continue to receive ototoxic treatments as a primary choice for therapeutic management, just as exposure to noise and ototoxins in the workplace will continue. Because both the risks and the consequences of noise- and ototoxin-induced auditory damage can be mitigated, these should be important priorities for audiological management.

This special issue of the *American Journal of Audiology* arose out of the 9th Biennial National Center for Rehabilitative Auditory Research (NCRAR) [VA RR&D C2361-C] national conference in Portland, OR, supported by the National Institutes of Health [1 R13 DC018228-01]. The conference was titled, “Ototoxicity and Noise Damage: Translating Preclinical Findings to Audiological Management,” and took place in September 2019. The NCRAR conference brought together over 150 stakeholders, including clinicians, researchers, and students from five countries to comprehensively address pertinent problems related to the prevention, diagnosis, and treatment of auditory disorders due to ototoxicity and/or noise. Attendees spanned a variety of ethnic and racial groups, with over 56% reporting a VA or DoD affiliation.

The objectives of this conference were to enhance knowledge of the mechanisms of auditory injury from ototoxins and noise overexposure and their relationships to theoretical models of tinnitus and hearing loss generation and to discuss how this knowledge can be translated into

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clinical practice. The overarching hypothesis of this conference was that clinicians and researchers will devise improved rehabilitative and pharmaceutical interventions if they can be shaped according to the specific auditory deficits, lesion sites, and individual patient priorities. Thus, a crucial aspect of the conference was to provide the patient's perspective by bringing in speakers who are themselves suffering from difficulties with speech perception and/or tinnitus secondary to noise or ototoxin exposure.

This special issue consists of 10 manuscripts that highlight information presented at the conference, and cover three broad themes that parallel the conference themes. The first theme is "Mechanisms." Peter S. Steyger's (2021) "Mechanisms of Aminoglycoside- and Cisplatin-Induced Ototoxicity" outlines multiple mechanisms of auditory damage resulting from treatment with aminoglycosides or cisplatin in a highly accessible and clinically pertinent manner. This article describes the trafficking routes of each drug, the resulting systematic damage of inner ear structures, and knowledge gaps that must be overcome to enable us to further refine ototoxicity management. Susan E. Griest-Hines, Naomi F. Bramhall, Kelly M. Reavis, Sarah M. Theodoroff, and James A. Henry (2021) provide insight into the types of noise exposure histories associated with auditory damage in their article, "Development and Initial Validation of the Lifetime Exposure to Noise and Solvents Questionnaire in U.S. Service Members and Veterans." Use of this questionnaire will no doubt be crucial for standardizing data collected in studies aimed at identifying risk factors for hearing loss, tinnitus, or hyperacusis in relation to noise and solvent exposure. In addition, the combined impacts of noise exposure and ototoxic chemicals among military Service members are addressed by Thais C. Morata, Michelle Hungerford, and Dawn Konrad-Martin (2021) in "Potential Risks to Hearing Functions of Service Members From Exposure to Jet Fuels." This article provides a brief synopsis of both hearing health policies and research related to noise-chemical interactions. The goal of this viewpoint is to assist audiologists in their decision making when providing care for populations who are routinely exposed to jet fuels. In "Review: Neural Mechanisms of Tinnitus and Hyperacusis in Acute Drug-Induced Ototoxicity," Richard Salvi, Kelly Radziwon, Senthilvelan Manohar, Ben Auerbach, Dalian Ding, Xiaopeng Liu, Condon Lau, Yu-Chen Chen, and Guang-Di Chen (2021) build on these articles to describe changes to the central auditory system that occur following peripheral auditory damage and how these changes are associated with tinnitus and hyperacusis. This article lays the foundation for an understanding of how auditory damage can manifest in deficits that extend past the audiogram.

The second theme is "Clinical Presentation." Included in this theme are two articles addressing the clinical presentation of ototoxicity in patients with CF. In their article, "Wideband Acoustic Reflex Growth in Adults with Cystic Fibrosis," Martha R. Westman, Daniel B. Putterman, Angela C. Garinis, Lisa L. Hunter, and M. Patrick Feeney (2021) describe how acoustic reflex growth functions differ in CF

patients treated with aminoglycosides compared with controls. This work contributes to the growing body of literature regarding methods of separating out outer hair cell dysfunction and synaptic/neuronal damage in clinical patients. The article, "Functional Impacts of Aminoglycoside Treatment on Speech Perception and Extended High-Frequency Hearing Loss in a Pediatric Cystic Fibrosis Cohort," written by Chelsea M. Blankenship, Lisa L. Hunter, M. Patrick Feeney, Madison Cox, Lindsey Bittinger, Angela C. Garinis, Li Lin, Gary McPhail, and John P. Clancy (2021), discusses metrics to determine the impacts of ototoxic treatments on speech perception. Speech perception difficulty is a key consequence of exposure to aminoglycoside medications and yet has rarely been characterized in the literature. This theme is further discussed in an article about the clinical presentation of noise-induced auditory damage from Naomi F. Bramhall, Garnett P. McMillan, and Amy N. Mashburn (2021), "Subclinical Auditory Dysfunction: Relationship Between Distortion Product Otoacoustic Emissions and the Audiogram," which uses statistical modeling to predict the audiogram from distortion product otoacoustic emissions (DPOAEs) in young Veterans with normal audiograms and demonstrates that discrepancies between DPOAEs and the audiogram may be related to cochlear synaptopathy. The last article for this theme is a viewpoint from Khaya D. Clark, Angela C. Garinis, and Dawn Konrad-Martin (2021), "Incorporating Patient Narratives to Enhance Audiological Care and Clinical Research Outcomes," which highlights several patients' perspectives on participating in their own clinical care decisions. This article argues for engagement of patients as key stakeholders in their experience of care processes for both clinical quality improvement projects and translational research.

The third theme is "Future Directions." In "Clinical Considerations for Routine Auditory and Vestibular Monitoring in Patients with Cystic Fibrosis," Angela C. Garinis, Gayla L. Poling, and Carmen C. Brewer, et al. (2021), along with numerous members of the International Ototoxicity Management Working Group (IOMG; see publication for complete author list), discuss optimal audiological monitoring strategies for patients receiving ototoxic therapies (e.g., those with CF). This is the first of several anticipated reports from the IOMG aimed at providing recommendations on how to implement an ototoxicity management program that addresses the needs of patients receiving specific ototoxic therapies and of the medical specialists that prescribe them. This theme is also discussed in Dawn Konrad-Martin, Keri O'Connell Bennett, Angela Garinis, and Garnett P. McMillan's (2021) article, titled, "A Randomized Controlled Trial Using Automated Technology for Improving Ototoxicity Monitoring in VA Oncology Patients." This article shows that a dedicated hearing surveillance program that uses the Oto-ID audiometer's automated mode improves adherence to ototoxicity monitoring protocols over a traditional service delivery model. The results demonstrate the need to consider accessibility when designing an ototoxicity management program for this

population and highlight the interest cancer patients have in obtaining aural rehabilitation services.

We are enthusiastic to present this special issue to the *American Journal of Audiology* readership and thank the numerous individuals who contributed to the conference and these publications. We hope this information will lead to improved clinical care in patients exposed to ototoxins and/or noise, as well as greater understanding of the associated underlying mechanisms. Cutting-edge research in these areas continues to develop, with a focus on patient-centered care and quality of life considerations. Thank you to the *American Journal of Audiology* and the audiology and hearing science community for your support.

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