Hearing health and care: The need for improved hearing loss prevention and hearing conservation practices

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Abstract—Hearing loss affects 31 million Americans, particularly veterans who were exposed to harmful levels of noise during military functions. Many veterans also receive treatment with ototoxic medications, which may exacerbate preexisting hearing loss. Thus, hearing loss is the most common and tinnitus the third most common service-connected disability among veterans. Poor implementation of hearing protection programs and a lack of audiometric testing during medical treatment leave veterans vulnerable to unrecognized and untreated hearing loss until speech communication is impaired. Individualized audiometric testing techniques, including assessment of high frequencies, can be used in clinical and occupational settings to detect early hearing loss. Antioxidants also may alleviate cochlear damage caused by noise and ototoxicity. Ultimately, hearing loss prevention requires education on reducing occupational and recreational noise exposure and counseling on the risks and options available to patients. Technological advances will improve monitoring, allow better noise engineering controls, and lead to more effective hearing protection.

Key words: antioxidant, auditory brainstem response, early detection, hearing conservation, hearing protection, noise-induced hearing loss, otoacoustic emission, ototoxic-induced hearing loss, prevention, tinnitus.

INTRODUCTION

Prevalence and Incidence of Hearing Loss

Whether referred to as a disability, disorder, or impairment, hearing loss is one of the most common chronic health conditions affecting all age groups, ethnicities, and genders. Hearing loss represents the third most prevalent health complaint in older adults following arthritis and stroke [1]. Results of the 2002 National Health Interview Survey estimate that nearly 31 million of all noninstitutionalized adults (aged 18 and over) in the United States have trouble hearing [2]. Additionally, many adults not included in the survey have hearing difficulties, particularly residents of nursing homes and active duty military personnel. Over 19 million individuals affected by hearing

disability are over the age of 45 [3], and one-third of Americans over age 65 have a hearing loss, mostly irreversible [4]. Furthermore, the Better Hearing Institute reports that nearly 50 million adults suffer from tinnitus, a ringing or buzzing that may or may not accompany hearing loss but is often an early indicator of hearing loss [5].

Age, excessive noise exposure, and treatment with ototoxic medications all contribute to the widespread hearing loss affecting more than 10 percent of the general population and a greater percentage of the adult population. Though a major health concern costing more than $30 billion a year in lost productivity, special education, and medical treatment [6], hearing loss is often minimized or ignored. Problems associated with vision are immediately addressed, monitored and treated, whereas hearing loss—preventable in many cases—receives far less attention. Only a few longitudinal studies have been conducted to determine the development and progression of hearing loss in the general population. In 2003 Cruickshanks et al. published results of a 5-year epidemiological study in which they monitored hearing loss among a group of adults aged 48 to 92 years, 1,635 of whom had no hearing loss at time of baseline evaluation and 1,085 had some hearing loss [7]. The 5-year incidence of hearing impairment was 21 percent and was higher among men than women (30.7% and 17%, respectively). Age was a significant risk factor for both incidence and progression of hearing loss, and more than half of those identified as having hearing loss at baseline examination experienced a progression in their hearing loss.

The incidence of hearing loss increases with age and is more prevalent among men than women by a nearly 2:1 ratio. According to public health statistics, the number of older adults is growing rapidly due to increased longevity, increased survival rates of illnesses and accidents, and aging of the "baby boomer" segment. Americans aged 65 and over currently comprise nearly 13 percent of the population but are expected to constitute 20 percent of the population in fewer than 25 years. Using U.S. Census Bureau figures, the Healthy People 2010 Program predicts that over the next 15 years, 78 million people in the United States will transition into the over-50 age group, further escalating the incidence of hearing loss well beyond its current proportion of 1 in 10 affected persons [8–9]. Clearly, this dramatic demographic shift will place unprecedented demands on all age-related healthcare concerns, particularly hearing healthcare.

According to the American Academy of Audiology [10], average, otherwise healthy individuals should benefit from normal hearing through at least age 60 if they take appropriate measures to protect their ears from dangerously high levels of noise. Thus, aging alone should not preclude average individuals from participating in communicative interactions throughout most of their lives. Unfortunately, the auditory system suffers premature injury as a result of lifestyle, employment, and medical treatment. One-quarter of all hearing loss in the United States can be attributed to harmful levels of noise exposure. Harmful levels of noise occur in the workplace, recreation, and environment due to poor noise control, inadequate hearing protection, and lack of education regarding the risks of hearing loss. In addition, there are more than 200 medications that can adversely affect hearing. Over 1 million Americans each year incur hearing loss from taking ototoxic drugs. Furthermore, noise exposure and ototoxic medications are synergistic, compounding damage and accelerating the natural decline of normal auditory function.

People depend largely on their sense of hearing to provide essential cues for carrying out fundamental activities of daily living. When hearing is impaired to the extent that it affects speech intelligibility, it can restrict employment and recreational and social activities. Hearing loss compromises an individual's safety by hindering appropriate responses to alarms and warning signals such as doorbells, smoke alarms, and sirens. Permanent hearing loss also contributes to psychosocial and physical health problems resulting in job and revenue loss, depression, and social isolation [11–12]. Such symptoms may continue despite costly and lengthy aural rehabilitation efforts. Data indicate an alarming increase in the prevalence and incidence of hearing loss at earlier stages in life, especially among men in the 35-to-60 age group [13]. Widespread implementation of prevention programs to reduce or eliminate preventable hearing loss is a tremendous public health need. Strategies for fulfilling this need include education on hearing loss prevention and research on causes of and evidence-based treatments for hearing loss, which can be translated into clinical practice.

Types and Causes of Hearing Loss

Three attributes must be ascertained to describe an individual's hearing loss: type of hearing loss (the location of the damage in the auditory pathway), degree of

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hearing loss (the extent to which hearing is impaired), and configuration of the hearing loss (the frequencies affected). Variations in the type, degree, and configuration of a person's hearing loss have an impact not only on the resultant communication impairment but also on the availability of potential treatment options. Moreover, early identification of hearing loss may provide avenues to preserve residual hearing abilities.

The three types of hearing loss or auditory system impairment are conductive, sensorineural, and central auditory processing disorders. When a conductive hearing loss occurs, sound waves are not effectively transmitted through the outer and middle ear to the inner ear. The most common causes of conductive hearing loss are partial or total occlusion of the ear canal within the outer ear; fluid within the middle ear as a result of colds, allergies, and ear infections (otitis media); and eustachian tube abnormalities. Conductive hearing loss often can be rehabilitated through medical or surgical intervention.

Sensorineural hearing loss occurs predominantly as a result of damage to hair cells in the cochlea, although it also may occur as a result of nerve cell damage within the nerve pathways between the inner ear and central auditory cortex. Exposure of unprotected ears to excessive levels of noise is a primary cause of sensorineural hearing loss. Other known risk factors include aging, a number of disease processes and illnesses, certain chemical agents, congenital disorders and injuries, genetic syndromes, hereditary susceptibility, therapeutic treatment with certain medications, tumors, and viruses. Sensorineural hearing loss cannot be rehabilitated through medical or surgical means and therefore represents a permanent hearing impairment.

Central auditory processing disorders occur when auditory centers and pathways in the central auditory cortex are damaged. Common causes of central auditory processing disorders include disease, traumatic brain injury, tumors, heredity, and yet unknown causes. Central auditory processing disorders also currently elude rehabilitation remedies.

Hearing sensitivity is most often described as the pure-tone thresholds of an individual's hearing thresholds at the traditional audiometric frequencies of 500, 1,000, 2,000, 4,000, and 8,000 Hz. The degree of hearing loss is described as the extent to which a person's thresholds exceed normal hearing (0–25 dB hearing level [HL]) and can significantly impact communication abilities and quality of life. Mild hearing losses (i.e., hearing thresholds

are elevated to 25–40 dB HL) can impact a person's ability to understand speech. The use of hearing aids may be appropriate for individuals with this degree of hearing loss, particularly children and employed or socially active adults. Moderate hearing losses (45–60 dB HL) often impose a mild-to-moderate hearing handicap on a person's ability to understand speech. Moderately severe hearing losses (60–75 dB HL) typically cause significant functional hearing impairment of a person's ability to understand speech. Severe (75–90 dB HL) and profound (90 dB HL or more) hearing losses are most often prohibitive to understanding speech unless remediated through such means as a cochlear implant.

The configuration of hearing loss is typically used to describe where an individual's hearing thresholds fall along a horizontal axis that represents the traditional speech frequency range, with lower frequencies first and higher frequencies later on the continuum. Thus, a sloping, high-frequency hearing loss configuration would describe the hearing impairment of an individual whose hearing thresholds are better at lower frequencies and progressively poorer at higher frequencies. This sloping, high-frequency configuration is commonly seen in age- (presbycusis), noise-, and medication-induced hearing losses, all of which tend to affect the higher-frequency regions first, then subsequently progress toward the mid- and lower-frequency regions. While some individuals are predisposed to presbycusis, hearing loss resulting from noise and ototoxic medications may be preventable if appropriate hearing preservation and early identification strategies are used. Implementation of hearing loss prevention methods is preferable to and more cost-effective than aural rehabilitation. Surprisingly, no systematic model for hearing loss prevention, conservation, or early identification of either noise- or ototoxic-induced hearing loss exists within the Department of Veterans Affairs (VA) or the majority of other healthcare institutions. Hence, evidence-based hearing loss prevention and hearing conservation strategies have not as yet been widely implemented as standards of practice for audiologists. Early detection of hearing loss is paramount to creating opportunities for behavior changes that can prevent further damage. It is imperative that hearing loss prevention, conservation, early identification, and best practices for hearing healthcare delivery, quality, and outcomes be developed and implemented across the VA healthcare system and the nation.

NOISE-INDUCED HEARING LOSS

While noise-induced hearing loss occurs in all age groups, working-age adults are particularly vulnerable. Occupational noise exposure affects more than 40 million Americans and is the most prevalent occupational hazard. The effects of occupational noise exposure can be exacerbated by noise in the environment (e.g., leaf blowers, music players, power tools) and can also be combined with age-related hearing loss, resulting in tinnitus and the reduced ability to hear and understand speech. Compromised auditory ability in speech communication and in sound localization and detection can pose a safety risk to affected individuals as well as to coworkers [14] and can affect revenue and employment rates for employers.

Veterans are at particular risk for having noise-induced hearing loss due to noise associated with military service [15–16]. The alarming incidence of hearing loss among World War II veterans contributed largely to the creation of audiology as a novel healthcare profession. While present military personnel benefit from improved weapons systems and armors that are increasing survival rates, regrettably noise-induced hearing loss is on the rise among U.S. servicemen and women. According to information reported at the 2004 Annual Force Health Protection Conference of the U.S. Army Center for Health Promotion and Preventive Medicine, hazardous noise exposure is higher than it was 30 years ago due to the intensity and magnitude of current operations, the extension of training and tours of duty, and the increase in the number of combat forces [17]. Among soldiers returning from deployments, hearing loss is the fourth leading reason for medical referral. One-third of soldiers who recently returned from deployments in Afghanistan and Iraq were referred to audiologists for hearing evaluations due to exposure to acute acoustic blasts; 72 percent were identified as having hearing loss. Auditory disabilities represented the most prevalent individual service-connected disability among veterans receiving compensation in fiscal year (FY) 2004, affecting some 742,211 individuals [18]. Nearly 375,400 of these veterans had a service-connected auditory disability at 10 percent or more and therefore received compensation benefits from the Veterans Benefits Administration (VBA) totaling more than $400 million. An additional 1,600,000 veterans had a secondary service-connected disability for hearing loss at less than 10 percent, which although not a compensable level, has created a tremendous demand for hearing healthcare services within the VA system. Among veterans with compensable service-connected disabilities, one in seven is service-connected for hearing loss and/or tinnitus, and the annual number of veterans who begin to receive compensation for hearing impairment continues to increase dramatically. According to the VBA, from 2000 to 2004, the number of veterans receiving compensation for hearing impairment increased 168 percent. In FY2004, the VA spent over $119 million to purchase 315,224 hearing aids. This amount does not include personnel costs associated with delivery of service and long-term patient management, which are estimated at approximately $300 million a year. Furthermore, more than $418 million in compensation benefits were paid to veterans specifically for tinnitus in FY2005. Combined compensation for auditory impairments, including hearing loss and tinnitus, exceeds $1 billion annually.

How Noise Exposure Affects Hearing

Sounds of sufficient intensity and duration can cause temporary or permanent threshold shifts regardless of the source of the sound. Temporary threshold shifts can result from moderate exposure and may be due to intracellular changes in the outer hair cells (OHCs) of the cochlea and swelling of the auditory nerve endings [19]. Moderate noise exposure may also cause temporary vascular, metabolic, and chemical changes, as well as a stiffening of the hair cell stereocilia, leading to a loss of hearing sensitivity [19]. Noise exposure is quantified as the total sound energy, a combination of sound intensity and duration, that reaches the inner ear. The Occupational Safety and Health Administration (OSHA) defines maximum exposure time for unprotected ears as 85 dB over a time-averaged, 8-hour workday. For every 5 dB increase in noise volume, the exposure time should be cut in half to minimize damage. For example, maximum exposure time should be 4 hours for a 90 dB sound and 7.5 minutes for a 120 dB sound. Lawn mowers (95 dB), airplane cabins (110 dB), and firearms (140 dB) are common sound sources that exceed these limits (**Figure 1**).

When recreational and environmental noise sources add to noise encountered in the workplace, significant irreversible damage to hearing can occur. Temporary threshold shifts are caused by intracellular metabolic and chemical changes in the OHCs. The stiffness of hair cell stereocilia can also decrease, which reduces the coupling of sound energy [19]. Recovery from temporary threshold shifts can occur if the noise exposure is not prolonged,
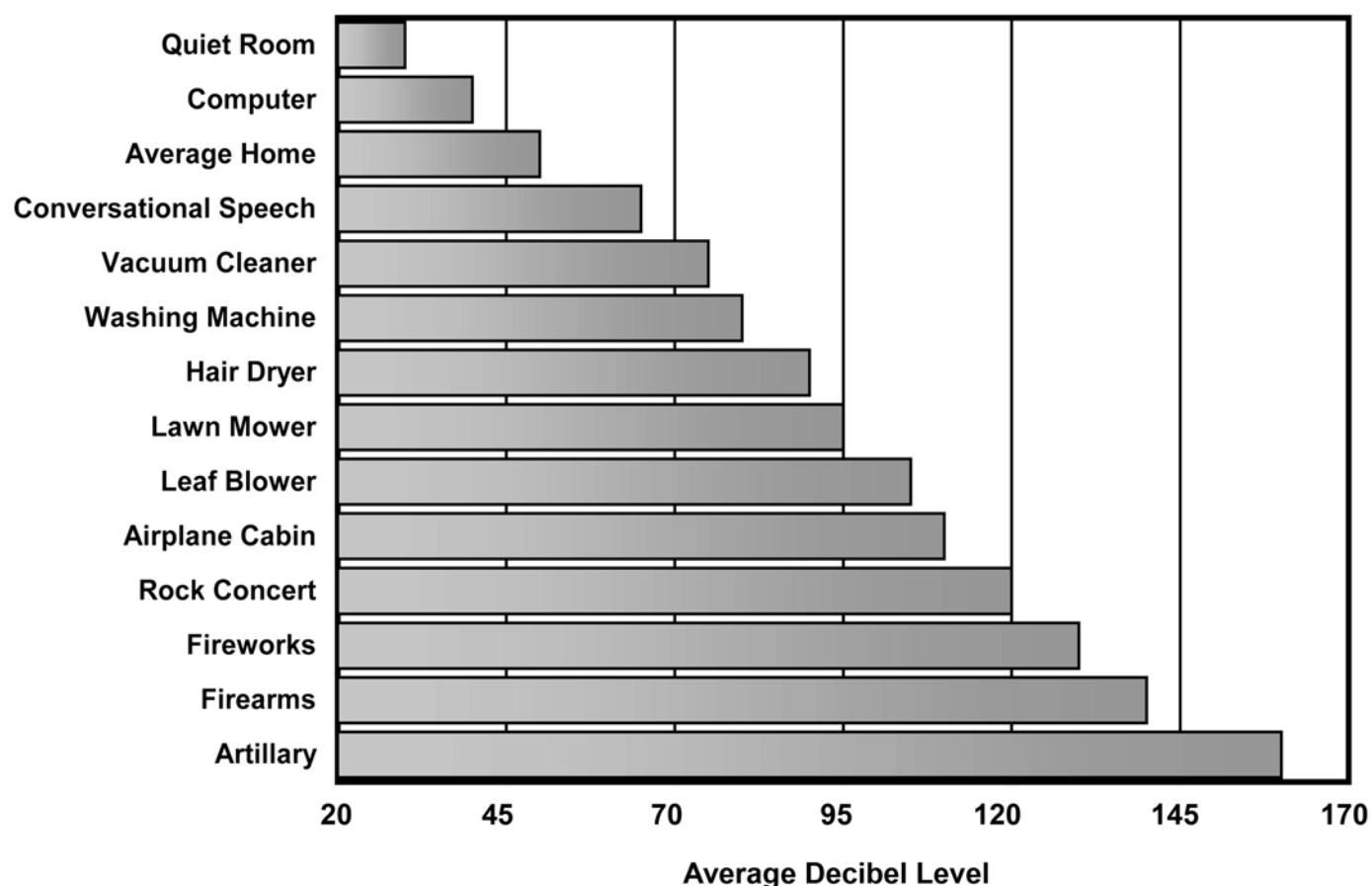
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Figure 1.
How loud is too loud? Average intensity levels in decibels of common sound sources.

although short exposures to sounds of sufficient intensity (such as explosions) can cause immediate, permanent hearing loss.

Permanent threshold shifts occur when sound duration and/or intensity produces permanent damage to the nerve fibers and the OHCs in the cochlea [20–21]. Continued exposure causes further cell damage, eventually leading to the degeneration of the corresponding nerve fiber. The rate of damage to the cochlea is greatest during the first 10 to 15 years of noise exposure and decreases as the hearing threshold increases [22], whereas age-related losses accelerate over time. Although noise exposure causes irreversible hearing loss, most research has been done retrospectively with large variability. In addition, the susceptibility of noise-induced hearing loss between individuals varies as much as 30 to 50 dB, possibly due to differences in ear anatomy and physiology, prior exposure to noise, and interactions of medications [19]. The

prevention of noise-induced hearing loss therefore requires control of exposure time and intensity, as well as individualized audiometric screening for hearing loss.

Noise-induced hearing loss can occur from steady state or intermittent exposure to loud noise or from a single impulsive exposure to a loud sound such as an explosion (acoustic trauma). Steady state noise exposure is usually symmetric leading to a bilateral sensorineural hearing loss, while some impulse noise, such as a gunshot, can produce an asymmetric loss. Both steady state and impulse noise exposures cause excessive oxidative stress and production of free radicals. A free radical is a molecule that exists naturally in an unstable state. To stabilize itself, the free radical takes available electrons from adjacent molecules that then become oxidized and therefore damaged. These changes lead to permanent cell damage in the inner ear. Exposure to ototoxic agents such as tobacco, solvents, or heavy metals may have a synergistic

effect on cell damage [23]. Damage to hearing from both steady state and impulsive noise exposures can also include tinnitus, which is a ringing, buzzing, or roaring sound sensation in the ears or head. Tinnitus can occur in one or both ears and may subside over time or continue throughout the affected individual's life. At least 15 percent of the U.S. population is affected by tinnitus, which often accompanies high-frequency hearing loss.

Exposure to noise with impulsive components, such as in steel construction, produces larger hearing losses than would be predicted on the basis of the level of steady state noise alone [24]. Kurtotic noise, a complex combination of continuous and impulsive noise, such as shipboard noise, causes more damage than either noise type alone because the effects of steady state and impulsive noises are synergistic [15]. In a study of the building construction industry, differences were found between groups exposed to the same sound energy levels but noise of different temporal characteristics [25]. Workers exposed to noise with impulsive components experienced greater hearing loss than those exposed to only steady state noise. In drop-forge factories, the hammer workers who were exposed to more impact noise had greater hearing loss than the weavers who experienced continuous noise [26]. Therefore, the effects of combined exposure to steady state and impulse noises are synergistic and cause greater noise-induced hearing loss.

Noise-induced hearing loss can be detected by conventional audiometry (250–8,000 Hz) and distinguished from age-related hearing loss. Audiograms typically show a noise-induced threshold shift from 3,000 to 6,000 Hz or a "notch" with recovery at 8,000 Hz [27]. This pattern is in contrast to the down-sloping audiogram of an age-related hearing loss. The noise-induced threshold shift may be attributed to the vulnerability of the base of the cochlea to noise exposure [28]. The location of the notch depends on the frequency of the damaging noise and the length of the ear canal [27]. As the hearing loss progresses because of continued noise exposure compounded by aging, the notch becomes less prominent, making audiometry to 8,000 Hz less diagnostic. Both steady state and impulsive noises have their largest effect above 12,000 Hz. Thus, early detection of noise-induced hearing loss should include frequencies to 20,000 Hz [29]. In addition, high-frequency sensitivity changes are not always accompanied by abnormal results below 8,000 Hz [30]. Steady state noise exposure typically produces smooth, symmetrical changes in the audiogram

above 12,000 Hz, while impulsive noise exposure presents as a change from 2,000 to 20,000 Hz with jagged, asymmetrical, high-frequency configurations [29].

Otoacoustic emissions (OAEs), recordable sounds that are reemitted by the cochlea, are also useful for detecting early changes in hearing sensitivity due to noise exposure. OAEs are related to normal function of cochlear OHCs and disappear when the cochlea is impaired. OAEs have been shown to be more sensitive and reproducible than conventional audiometry [31]. In a study of pilots, OAEs diminished with increased noise exposure; as flight times increased, the pilots' high frequencies were initially affected followed by middle and low frequencies [32]. Eleven percent of the pilots had no significant changes in OAEs. Therefore, individual susceptibility and resistance to noise-induced hearing loss vary. OAEs have value as an effective tool for identifying damage from noise exposure and for investigating hearing preservation.

Hearing Conservation and Prevention

Although noise-induced hearing loss is permanent, previously damaged ears are not more sensitive to future exposure and the damage does not progress once exposure stops [22]. Therefore, with audiometric screening, education, and prevention, noise-induced hearing loss should be reduced or eliminated. OSHA standards currently require that hearing conservation programs be initiated when noise levels equal or exceed 85 dB and that an individual who experiences a 10 dB threshold shift from baseline in a pure-tone average of 2,000, 3,000, and 4,000 Hz should receive prospective audiometric monitoring. Hearing conservation programs include engineered controls and personal hearing devices (usually earmuffs or plugs) to reduce noise levels and administrative scheduling to limit time in loud areas. Because noise controls are only required if technically and economically feasible [33] and time limits may not be cost-effective, such as in the case of mining, only personal hearing protection devices are consistently used. The consistent use of hearing protection devices is therefore the most important behavioral change that a person can make to prevent noise-induced hearing loss [34]. The most reliable predictors of hearing loss are the percentage of time that hearing protection is worn [35] and the proper fit of the protection [36]. However, the effectiveness of hearing protection programs is hindered by poor compliance in the use of hearing protection devices due to communication difficulties, comfort issues,

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individuals' attitudes about protecting themselves from noise-induced hearing loss, and individuals' perceptions about how others who do not use hearing protection will view them if they choose to use hearing protection [37–39]. Failure to use hearing protection for just 30 minutes during the workday reduces the protective device's effectiveness in preventing hearing loss by 50 percent [40]. Furthermore, hearing protection devices have inherent limitations including noise exceeding the protective limits of the device, fit problems, unexpected short exposures to loud noises, damaging acoustic energy transmitted by bone conduction that bypasses the hearing protection device, and the combined and potentially synergistic effects of noise plus ototoxic solvents or heavy metals.

While noise-induced hearing loss primarily targets the adult population, a disturbing increase in incidence of noise-induced hearing loss among today's youth has occurred. Results of the Third National Health and Nutrition Examination Survey revealed that among 6,166 youth between 6 and 19 years who received audiometric testing during a 6-year period, 14.9 percent had a hearing loss in one or both ears [41]. Subsequently, Niskar et al. estimated the prevalence of noise-induced hearing threshold shifts among U.S. children aged 6 to 19 to be 5.2 million [42]. Similarly, in 1992 Montgomery and Fujikawa reported that the percentage of second graders with hearing loss had increased 2.8 times (280%) over a 10-year period, and the percentage of eighth graders increased over 4.0 times (400%) during the same period [43]. The Hearing Alliance of America reports that 15 percent of college graduates have a level of hearing loss equal to or greater than their parents [44]. Perhaps not coincidentally, the number of children playing with loud electronic gadgets and toys and young adults listening to stereos and portable music devices (e.g., walkmans and MP3 players) at high volumes is increasing.

Hearing conservation programs that are tailored to school-age children and deliver early and repeated education regarding hearing and hearing loss are necessary to establish consistent use of hearing conservation practices. Children and parents should be educated on protective measures to prevent hearing loss at home and school and during social and recreational events. Hearing conservation programs should include an explanation of—

1. Normal auditory function.
2. Types and causes of hearing loss.
3. Dangers of excessive noise exposure.
4. Warning signs of noise-induced hearing loss.

5. Hearing loss prevention strategies [45].

In addition to school curricula, community-based educational programs such as Dangerous Decibels® (Oregon Hearing Research Center) and WISE EARS!® (National Institute on Deafness and Other Communication Disorders) communicate the importance of hearing protection to all age groups.

Hearing conservation programs in the workplace and in the general population seek to increase compliance and effectiveness of hearing protection protocols through audiometric screening tests and education on the dangers of noise exposure. Evidence has suggested that tailored, multimedia hearing loss prevention programs can improve attitudes, knowledge, and behavior concerning the prevention of hearing loss. An effective hearing loss prevention program consists of—

1. Audits performed to determine needs of work environment, labor, and management.
2. Assessment of noise exposures.
3. Engineering and administrative control of noise exposures.
4. Audiometric evaluation and monitoring of hearing.
5. Appropriate use of personal hearing protection devices.
6. Education and motivation.
7. Record keeping.
8. Evaluation of program effectiveness [46].

To further encourage conservation practices, effective prevention programs should address factors associated with individual perceptions of vulnerability, seriousness of the hearing loss threat, and benefits to be gained from participation [47].

While eliminating or producing barriers to harmful noise is the best line of defense against noise-induced hearing loss, metabolic changes on a cellular level may prevent damage to the cochlea. The use of antioxidants has been shown to attenuate the effects of noise exposure [48]. Histopathological damage is often due to the presence of free radicals, which deplete the key cochlear antioxidant glutathione. Glutathione helps to eliminate foreign substances, making it one of the body's major antioxidant defense systems. The reduction of glutathione leads to the accumulation of reactive oxygen species, highly unstable molecules including free radicals derived from the metabolism of oxygen, which permanently damage the cell [48–50]. L-carnitine, which has been used as a dietary supplement and a treatment for neurodegenerative disease, was shown to reduce noise-induced threshold shifts and limit both

inner and OHC loss [50]. Although less effective, the over-the-counter nutritional supplement N-acetylcysteine was also shown to counteract oxidative stress by replenishing intercellular glutathione levels in the cochlea, thus preventing cell damage [51]. In the future, administration of an oral supplement before noise exposure may prove to effectively reduce cell damage. In addition, many nutritional antioxidants such as magnesium (from fish, almonds, and spinach), D-methionine (from fermented proteins such as cheese and yogurt) and reservatrol (from red wine and grape juice) act as direct antioxidants that increase glutathione levels and protect critical enzyme levels [52]. D-methionine is particularly effective because it not only eliminates free radicals but also increases glutathione and slows its efflux from the injured cell [50]. New developments in cell damage prevention coupled with employee education and the use of hearing protection could significantly reduce noise-induced hearing loss.

OTOTOXIC-INDUCED HEARING LOSS

Another leading cause of preventable sensorineural hearing loss is therapeutic treatment with potentially ototoxic medications [53]. Ototoxic agents are commonly prescribed to aggressively treat various infections and cancers, with the desired outcome of extending patients' lives. Approximately 4 million patients in the United States are at risk for hearing loss from aminoglycoside antibiotics (such as gentamicin) each year, with many more potentially affected by platinum-based chemotherapy agents (such as cisplatin). Nearly 200 prescription and over-the-counter drugs are recognized as having ototoxic potential [54]. **Figure 2** contains many of the most commonly used medications with ototoxic potential [55]. The VA Pharmacy Service estimates that over 100,000 veterans hospitalized in the VA healthcare system during 2002 received therapeutic treatment with ototoxic drugs. A significant percentage of patients receiving ototoxic drugs experience hearing loss. In addition, loop diuretics, often prescribed for congestive heart failure, renal failure, cirrhosis, and hypertension, can cause ototoxicity. Furthermore, coadministration of loop diuretics and aminoglycoside antibiotics may have a synergistic effect on ototoxic hearing loss [56]. The likelihood of preexisting hearing loss places veterans treated with ototoxic drugs at an even greater risk; that is, further loss of hearing can immediately exacerbate communication impairment and

reduce posttreatment quality of life. Thus, prospective audiometric testing and the early identification of ototoxic hearing loss are critical to facilitating alternative treatments, wherever possible, that can minimize or prevent communication impairment.

Damage to cochlear and/or vestibular function as a result of ototoxicity can be temporary, although it is usually permanent. Medications cause oxidative stress when the generation of free radicals interferes with the antioxidant defense system. Oxidative stress, in turn, damages the cells of the inner ear. Clinical complaints related to ototoxicity are those commonly associated with hearing loss, such as tinnitus and difficulty understanding speech, particularly in a noisy environment. However, immunosuppressed and infectious disease patients, particularly children, are especially susceptible to otitis media and may present with hearing changes not associated with ototoxic medications. Spinning vertigo is also a hallmark of ototoxic damage [56–57], although this symptom can result from nonototoxic factors such as malaise, poor nutrition, nephrotoxicity, and nausea and vomiting caused by chemotherapy.

Symptoms resulting from ototoxic changes can present days or even months after administration of the ototoxic drug [56]. Because these symptoms are poorly correlated with dosage [57], peak serum levels [58], and other toxicities (e.g., renal toxicity [59]), the only way a clinician can detect ototoxicity is by directly assessing auditory and vestibular function. Initial detection of ototoxic damage varies greatly. Significant hearing loss can follow administration of a single dose in one patient while others may not experience symptoms for weeks or even months after treatment [57,60]. Patients may not notice ototoxic hearing loss until a communication problem becomes apparent, signifying that hearing loss within the frequency range important for understanding speech has already occurred. Similarly, by the time a patient complains of dizziness, permanent vestibular system damage probably has already occurred.

Early ototoxicity investigations involving animals demonstrated that initial detection of ototoxicity typically corresponded with damage to hair cells in the basal region of the cochlea, where higher frequency sounds are processed. Results of clinical studies in individuals administered ototoxic drugs [61–64] and in animal models of ototoxicity [65–67] demonstrate that ototoxic damage progresses from high to low frequencies. For this reason, hearing assessment at the highest audible frequencies for

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Aminoglycoside Antibiotics	Antineoplastic Drugs
Amikacin	Cisplatin
Gentamicin*	Carboplatin
Neomycin*	Nitrogen mustard
Kanamycin	Methotrexate*
Netilmicin	Vincristine
Streptomycin*	Dactinomycin
Tobramycin*	Bleomycin
Other Antibiotics	**Antimalarial Drugs**
Erythromycin*	Quinine*
Vancomycin	Chloroquine
Chloramphenicol	Hydroxychloroquine*
Furazolidone*	Primaquine*
Polymyxin B and E	Quinidine*
Trimethoprim-sulfamethoxazole	Pyrimethamine
Loop Diuretics	**Salicylates**
Ethacrynic acid*	Aspirin
Furosemide*	Nonsteroidal anti-inflammatory agents
Bumetanide*	

Figure 2.
Commonly used medications with ototoxic and also *vestibulotoxic potential. *Adapted from:* Seligmann H, Podoshin L, Ben-David J, Fradis M, Goldsher M. Drug-induced tinnitus and other hearing disorders. Drug Saf. 1996;14(3):198–212.

each patient not only allows early detection of ototoxic changes but also is critical for the detection of hearing changes before the lower frequencies necessary for understanding speech are affected.

Exposure to excessive noise can exacerbate the effects of ototoxicity. Noise exposure prior to treatment with an ototoxic drug does not appear to affect the potential for ototoxicity [68]; however, excessive noise concomitant with treatment can cause an enhanced ototoxic effect [69]. Documentation exists showing the potentiating effect of noise associated with aminoglycosides [70] and cisplatin [71]. A further concern is that noise exposure following treatment can act synergistically with aminoglycosides that have not fully cleared from the inner ear [72].

Measures of Ototoxicity

Despite evidence supporting the importance of early identification of ototoxicity, monitoring programs are not commonplace in hospitals and clinics. This lack of program implementation may be due in part to the time-consuming and labor-intensive procedures required to complete the testing protocol. For widespread acceptance and use, early ototoxicity identification techniques need to

be efficient and cost-effective and maintain a high degree of intrapatient reliability, sensitivity, and specificity.

Extending audiometric testing to include frequencies from 9,000 to 20,000 Hz is the most effective way to detect the early stages of ototoxicity [73]. The VA Rehabilitation Research and Development (RR&D) Service, National Center for Rehabilitative Auditory Research (NCRAR), has developed methodology for conducting reliable high-frequency testing [74]. This finding contributed to the American Speech-Language-Hearing Association's (ASHA) publication of "Guidelines for the audiological management of individuals receiving cochleotoxic drug therapy," which recommended testing frequencies from 9,000 to 20,000 Hz [73]. For patients who can provide reliable behavioral responses, pure-tone audiometric data is collected at the highest frequencies, progressing to the lowest frequency at which a response can be obtained. Numerous studies have demonstrated that monitoring of behavioral thresholds at frequencies between 250 to 8,000 Hz and 9,000 to 20,000 Hz is a sensitive indicator of ototoxicity [62–64] but is lengthy and labor-intensive.

Data have revealed that a limited number of frequencies are typically involved in the initial detection of ototoxic

threshold changes [75]. In collaboration with Virtual Corporation, a computer-based Model 320 audiometer was modified to enable hearing threshold evaluation in one-sixth octave intervals up to 20,000 Hz, permitting the discovery of a patient-specific "sensitive range for ototoxicity" (SRO). An evaluation protocol using one-sixth octave steps within a seven-frequency range (spanning one octave) identified the individualized SRO. Monitoring for early indications of ototoxicity with only the individualized SRO reduced testing time by at least two-thirds while maintaining 90 percent sensitivity to initial ototoxic threshold changes when compared with evaluation at both conventional and high frequencies. A test protocol targeting the SRO in one-sixth octave increments has proven to be a sensitive, reliable, and time-efficient behavioral strategy for early detection of ototoxicity whether the SRO falls above [75–76] or below [77] 8,000 Hz.

Identifying an individualized SRO has the potential to optimize auditory rehabilitation for veterans and other individuals treated with ototoxic medications. Despite this discovery of a clinically efficient, sensitive, and reliable shortened protocol, no portable audiometers capable of evaluating hearing thresholds in one-sixth octave steps are available commercially. The NCRAR is currently developing a portable, handheld device based on the behavioral threshold SRO concept. The device will be an inexpensive, computer-automated system sensitive to ototoxicity early detection and suitable for both onsite (hospital wards and clinics) and distant site (other hospitals, clinics, and patients' homes) testing by audiologists, other healthcare professionals, and patients themselves. Ultimately, the computer automation of this system will permit remote transmission of test results to a centralized database for analysis, interpretation, and follow-up. Advances of this nature can make ototoxicity early detection a standard of healthcare for patients throughout the nation.

Audiometric behavioral testing allows early ototoxicity detection for most patients. However, many hospitalized patients receiving ototoxic drugs are unable to respond reliably to behavioral tests and, consequently, are not monitored for ototoxicity. The risk for hearing loss is expected to be similar for patients who can and cannot respond reliably; however, for patients who cannot be tested behaviorally, early detection of ototoxicity and alteration in drug treatment are not possible. Accordingly, these patients are at a greater risk of undetected hearing loss than patients who can be tested behaviorally. Thus, a clear need exists for nonbehavioral, objective techniques such as auditory evoked potential (AEP) and OAE to test hearing sensitivity.

AEP consists of an electrophysiological response from the ear (VIIIth nerve or auditory centers located in the brain) that is provoked by an auditory stimulus and measured by electrodes placed on the scalp/forehead and behind the ears. AEPs can reveal differences in hearing threshold, wave morphology, and/or latency in subjects receiving ototoxic agents, thereby indicating the occurrence of ototoxicity. Significant elongation and/or disappearance of wave V latencies were concomitant with diminishing hearing in early studies by Bernard et al. [78], who studied neonates treated with aminoglycoside, and by Piek et al. [79], who studied comatose adult patients receiving aminoglycosides. These studies demonstrate that AEPs are effective monitoring tools for nonresponsive individuals but are limited to 4,000 kHz and below. Hearing loss could thus progress to the point of communication impairment before being detected by AEP with conventional click stimuli. Tone bursts used to obtain frequency-specific responses have substantially increased the usefulness of AEP [80–84]. Specifically, high-frequency tone bursts (8,000–14,000 Hz) allow detection before the speech-frequency range is affected. AEP testing using high-frequency tone burst stimuli has shown good intra- and intersession test-retest reliability, a requirement for serial monitoring of ototoxicity [82], and more sensitivity than conventional clicks in the detection of ototoxicity [85] in patients with measurable hearing above 8,000 Hz. High-frequency, multistimulus tone burst trains (the presentation of tone bursts in multiple sequences) in AEPs have been shown to increase efficiency by reducing test-time by 77 percent [86] and 80 percent [87] while maintaining reliability, although lengthy setup times and lack of portability hinder applicability.

OAE testing is another nonbehavioral or objective measure that has been used for early detection of ototoxicity. OAE generation depends upon the physiological status of the OHCs, which is compromised by most ototoxic drugs [88]. OAEs can be elicited by clicks or tonal signals. Responses to clicks or tone bursts are referred to as transient evoked OAEs (TEOAEs), whereas responses elicited using two tones presented simultaneously are called distortion product OAEs (DPOAEs). Emissions elicited by single-tone stimuli are called stimulus frequency OAEs (SFOAEs). SFOAEs at low and moderate stimulus levels generated by a single mechanism [89–90] are most analogous to full (conventional and ultrahigh) frequency pure-tone behavioral testing, which remains the gold standard for

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ototoxicity early detection. Considerable literature exists with respect to TEOAE and DPOAE, and these tests have been used in studies with limited numbers of subjects to detect ototoxicity.

Clinical studies in humans and experimental studies in animal models have established a link between drug-induced changes in TEOAE or DPOAE responses and changes in the cochlear OHCs [91]. Most human studies have examined ototoxic changes in OAE level in two distinct populations: children with cystic fibrosis receiving aminoglycoside antibiotics [92–93] and adults with cancer receiving the platinum-based drug cisplatin [94]. In many cases, ototoxic changes in behavioral audiometry occurred later than OAE changes, or not at all. Behavioral testing within the ultrahigh frequency range showed effects of ototoxicity in a similar proportion of ears compared with OAE testing [95]. Similar to behavioral ototoxic changes, the highest frequencies at which a DPOAE response can be elicited also appear to be those most sensitive for early detection of ototoxicity [95–96].

Advantages of using DPOAEs as objective measures of ototoxicity include their frequency specificity and their measurability over a fairly wide frequency range. Testing can be performed rapidly at a patient's bedside with good test-retest reliability. Drawbacks of OAE measures include limited frequency range (generally up to about 8,000 Hz), insufficient output for stimuli above 8,000 Hz, and increased system distortion at the higher frequencies. In addition, standard calibration procedures may produce errors at high frequencies and differences in probe-insertion depth add variability. The biggest problem with OAEs is that changes in hearing sensitivity, where thresholds are already poor at baseline, may not be detectable with DPOAE measures because DPOAE levels are only linked to hearing sensitivity for thresholds less than about 60 dB SPL and hearing loss may preclude obtaining measurable responses.

Prevention of Ototoxic-Induced Hearing Loss

When a life-threatening illness warrants treatment with ototoxic drugs, preserving the quality of the patient's remaining life is typically a treatment goal. Early detection of ototoxic hearing loss provides physicians with the critical information and opportunity necessary to minimize further damage and, in some cases, prevent hearing loss from progressing to the point that aural rehabilitation is required. Ototoxic damage that progresses undetected or without

consideration of alternative treatment regimens may have severe vocational, social, and interpersonal consequences.

A successful ototoxicity monitoring program must emphasize early identification to enable physicians, medical personnel, and patients to make informed decisions related to ototoxic medications and their effects. Audiologists are integral in this process. If an ototoxic hearing change is identified, potential treatment options the physician may consider include—

1. Changing the drug to one that has a reduced risk for ototoxicity.

2. Stopping treatment.

3. Altering the drug dosage.

Conversely, if no change in hearing is detected, the physician may opt to treat the patient more aggressively. The early detection of ototoxicity may prevent or reduce hearing damage that could have a devastating effect on communication and posttreatment quality of life.

Current research has focused on the many antioxidants and free radical scavengers that can mitigate the overall toxicity of potentially ototoxic medications. Some medications act by inducing free radical damage on target cells [52]. Antioxidants may reduce cell damage to normal cells by counteracting reactive oxygen species and increasing glutathione levels [52]. Many otoprotectants have been studied including sodium thiosulfate [96–97], amifostine [98], and diethyldithiocarbamate acid [99], although many of these chemicals were found to interfere with the efficacy of cisplatin [100–101]. Salicylates are effective chemoprotectors because they modify the serum levels of gentamicin without altering the efficacy of the drug [102–104] and intervene in the pathways that lead to cell death. When salicylates are coadministered with cisplatin, antioxidant levels are elevated and threshold shifts reduced [103]. D-methionine [105], N-acetylcysteine [106], and vitamin E [107] also appear to have protective affects against ototoxicity by inactivating free radicals. In addition, D-methionine, N-acetylcysteine, and L-carnitine may work as "rescue agents" that can be administered after a toxic event to prevent permanent damage [52]. Reducing the incidence and severity of adverse effects could permit the administration of higher, possibly more effective, doses of antitumor drugs. Direction of this research is particularly important because standardized methods of measuring ototoxicity are essential in describing the chemoprotective qualities of the drugs under study. Further research in chemoprotectants may enhance the understanding of the mechanisms of ototoxicity,

potentially leading to otologically "harmless" medications and better techniques for managing illness.

Patient Education

Patient education is an additional element necessary for achieving effective ototoxicity prevention, identification, and monitoring. Audiologists should include three different phases of patient education. First, the audiologist must initiate contact with patients and educate them regarding potentially ototoxic drugs and the importance of ototoxicity early identification and monitoring. Additionally, audiologists must provide counseling regarding the risks of hearing loss associated with treatment to help prepare patients to have realistic expectations regarding symptoms, including hearing loss and tinnitus [55,108]. Finally, audiologists must emphasize the importance of hearing protection during and following therapeutic treatment and advise patients of the increased vulnerability of the auditory system during treatment with ototoxic drugs. Since ototoxic damage of the cells is compounded by noise exposure and risk or susceptibility to noise-induced hearing damage is increased, audiologists must urge patients to avoid excessive noise exposure during treatment. Potentially ototoxic medications can remain in the cochlea long after therapy has ended, so it is also important for audiologists to instruct patients to avoid noisy environments for six months after therapy completion because they remain more susceptible to noise-induced cochlear damage [70,108]. Following treatment with ototoxic medications, patients should participate in hearing conservation and prevention programs in which they are advised to wear appropriate hearing protection when exposed to excessive noise. Early education by audiologists about ototoxic hearing loss is essential and provides an opportunity to counsel the patient and family regarding communication strategies and protection from noise and to perform any necessary rehabilitation.

CONCLUSIONS

For most people, the sense of hearing is not only a critical portal for language allowing for communication with others but is also a vital element for staying oriented within the environment. Thus, audition is a defining element of quality of life. The Better Hearing Institute (www.betterhearing.org) has compiled data supporting the prediction that between 1990 and 2050 the number of people afflicted with hearing impairment will grow at a faster rate than the total U.S. population [5]. When hearing is impaired to the extent that speech intelligibility is affected, social interaction, employment, and recreational activities can become restricted. Permanent hearing loss can lead to psychosocial and physical health problems that result in job and revenue loss, depression, and social isolation—symptoms that may persist despite costly and lengthy aural rehabilitation efforts. No person should have to suffer unnecessary hearing impairment, particularly as a result of employment or medical treatment. Current scientific knowledge, however, is insufficient to predict whether any particular individual will incur noise- or ototoxicity-induced hearing loss. Unfortunately, approximately 10 million people in the United States currently have a hearing loss attributable to harmful levels of noise exposure from the workplace, recreation, and/or environment. Each year, an additional 1 million Americans incur hearing loss as a result of taking ototoxic drugs, and the synergistic effects of noise exposure and ototoxic medications accelerate and compound damage to the auditory system. From a public health perspective, widespread implementation of prevention strategies to alleviate, whenever possible, hearing impairment and the resultant disabling conditions is needed. Prevention can be accomplished through research on causes of and evidence-based treatments for hearing loss, the results of which can be translated into practice, and through improved education and consumer guidance regarding the risks of hearing loss, appropriate noise controls, and hearing protection practices.

While best practice procedures for hearing loss prevention and hearing conservation by early identification exist in other sectors including the Department of Defense and some private industry settings, the VA and the majority of other medical care institutions lack systematic models and system-wide implementation. The associated communication disabilities individuals with hearing loss encounter often render them socially disadvantaged or isolated and with a compromised quality of life. The VA and the national public health community bear the ethical and professional responsibility to ensure that patients receive appropriate hearing loss prevention and hearing conservation interventions to avoid or minimize preventable hearing losses. In addition, hearing loss protection programs must be maintained in the workplace to eliminate noise-induced hearing loss.

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