DISORDERS

MEDICATIONS

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ARTICLE

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Ototoxicity

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WHAT IS OTOTOXICITY?

Ototoxicity refers to the ability of a substance to be potentially toxic to the ear tissues. These substances may be harmful to the cochlea (i.e., "cochleotoxic")—affecting the organ responsible for hearing within the inner ear, and/or harmful to the vestibular system (i.e., "vestibulotoxic")—affecting the balance sensors in our ear that are important for detecting head rotation and help us maintain equilibrium [9].

EXPOSURE TO OTOTOXIC AGENTS

The effects of ototoxic agents gained recognition among medical professionals after the use of antibiotics in World War II [53]. Over the next several decades, the pharmaceutical industry has evolved rapidly, and billions of dollars have been poured into drug research and development. As a result, there has been an explosion in the number of potentially ototoxic substances [26]. There are more than 600 known categories of drugs with the potential to cause ototoxicity [13].

Ototoxicity usually occurs through environmental exposure to harsh workplace chemicals or as part of treatment for serious, life-threatening illnesses such as cancer and infection [61]. In the workplace, industries that are prone to ototoxic exposure include manufacturing, mining, construction, and agricultural operations. Examples of job types at higher risk include metals fabrication, machine shop work, leather tanneries, textile mills, petroleum refineries, paper mills, chemical plants, plastics manufacturing, furniture plants, mass transit operation and maintenance, electrical device manufacturing, and industries that use solar cells. More industries and chemicals are continually being identified and examined, but many of these susceptible job types go unrecognized.

When there is a disturbance to hearing and/or balance, the exact cause is not always identified. Uncovering the source in the workplace usually requires extensive investigation, and efforts are then directed toward prevention of future exposure [68].

In medical treatments, these substances are often used because there is not a safer or more effective alternative to treat the illness [24, 63]. Ototoxic drugs are also

sometimes discovered or used in experimental clinical trials. Clinical trials are studies that are designed to evaluate the safety and effectiveness of new medical treatments. Clinical trials usually take place after substantial laboratory study, and represent initial efforts to understand the treatment effect of a drug in humans [39].

Regardless of the exposure source, ototoxic substances can have long-term consequences for a variety of health-related and social outcomes [44].

COCHLEOTOXICITY

The human ear is a complex system comprised of several different parts that can be divided into three sections—the outer ear, middle ear, and inner ear. The outer ear is responsible for amplifying and directing sound toward the eardrum. The eardrum receives the sound waves and transfers the energy through the middle ear with the help of tiny bones called ossicles. The middle ear passes the sound waves to the fluid-filled inner ear organ called the cochlea. Once in the inner ear, sound vibrations travel along the length of the fluid-filled cochlea. This results in a cascade of chemical changes within the hair cells that cause release of neurotransmitters, and a nerve impulse that is sent to the brain for interpretation.

Ototoxic substances can damage and interfere with this complex system in a variety of ways. Though the mechanisms of each drug can vary, some common ways ototoxic drugs can affect the ear include:

1. Damaging the delicate hair cells of the inner ear;
2. Disrupting the signal neurotransmitters needed for turning sound from a chemical signal into an electrical one;
3. Changing the composition of fluid or nutrients supplying the ear;
4. Compromising the integrity of the auditory nerve fibers themselves.

Damage caused by drugs that affect signal communication or neurotransmitters is often reversible. However, drugs that cause structural deterioration result in permanent damage as these auditory structures do not regenerate in humans. Regardless of permanence, ototoxic hearing loss can substantially impact communication abilities and quality of life [41].

Changes in hearing from ototoxicity often impact the high frequency sounds [26]. Hearing loss in these frequencies typically presents itself as difficulty hearing in background noise, needing to ask speech partners for repetitions in conversation, feeling like the volume needs to be louder to hear clearly, and difficulty hearing women and children who may have higher-pitched voices.

Other symptoms include:

1. Tinnitus (ringing, chirping, buzzing, etc.);
2. Hyperacusis (heightened sound sensitivity); and
3. Feelings of ear fullness [13].

Some of the physical and nerve pathways continue to mature through infancy and childhood, making young children particularly vulnerable to ototoxic exposure [44]. In children, even minimal hearing loss can delay speech and language development, cause poor performance in school, and alter social functioning [26].

VESTIBULOTOXICITY

Studies on ototoxic effects have primarily focused on damage to the cochlea, with little attention paid to the vestibular system. This is likely due to the wider availability of audiometric testing compared to vestibular function testing [61].

Symptoms of vestibular loss due to ototoxicity are variable, but include:

1. Oscillopsia (blurry vision with head movement);
2. Dizziness;
3. Motion sickness;
4. Unsteadiness when walking (especially in the dark or on dynamic surfaces like grass, gravel, uneven pavement, etc.) [1, 5, 35];
5. Falls;
6. Reduced mobility; and
7. Low quality of life [36].

When severe, this can negatively affect the ability to complete routine daily tasks and threaten independent functioning.

The causes of vestibular loss are varied and not always easy to identify [61]. The main targets of these chemicals are usually the delicate vestibular hair cells, [65]. While hearing loss is easier to recognize, many patients may confuse vestibular loss as part of disease progression, attribute it as byproduct or symptom of another known problem in their medical history, or as natural deterioration of general health status with aging. Additionally, the visual and proprioceptive systems can compensate for vestibular deficits if damage occurs, further muddying the clinical presentation of vestibular

symptoms. This sometimes gives patients the experience of spontaneous improvement. For these reasons, vestibulotoxicity is likely underdiagnosed by clinicians and continues to be a challenge within healthcare systems [61].

WHO IS AFFECTED BY OTOTOXICITY?

Ototoxicity affects individuals of all age groups. Although the effects are well-documented, the global impact of these substances is unknown [26]. Prevalence of ototoxicity ranges widely, from 4% to 90% [16, 29, 40, 43, 45, 55, 64].This is due to the varied criteria used to define and measure ototoxicity and other situational factors including: the type of ototoxic substance, cumulative dosage over time, and how the drug is delivered to the targeted tissues (e.g. a pill vs. injection) [44].

Populations at elevated risk of harmful side effects are children and those who have received high, cumulative doses of ototoxic agents over time [40, 43, 46, 64, 67]. Individual variability in response to these chemicals comes from genetic susceptibility, as well as other factors such as age, gender, ethnicity, geographic location, bioavailability (how much of the substance dose makes it to circulation within the body), treatment duration, and other chronic health conditions such as congestive heart failure, renal failure, and hypertension.

Further complicating prevalence reports are the varied methods of audiological protocols used for evaluation and monitoring, and a lack of appropriate referral for ototoxic symptoms since these may be reversible or non-life-threatening [26]. All of these factors support the argument that the potential impact of these drugs should be determined on an individual basis—there is no perfect theoretical model that can be applied to every person.

COMMON DRUG CLASSES KNOWN TO CAUSE OTOTOXICITY

With more than 600 ototoxic drug classes known to potentially harm the ear, and even more being developed, detail for each drug class is beyond the scope of this article [13]. While the mechanisms and actions of many drugs are known, it is sometimes difficult to distinguish the exact source of ototoxicity when these substances are used in conjunction with other medications and treatments. Many of these drugs are rarely used alone [61]. For these reasons, this article will touch briefly on some of the common drug classes known to be ototoxic, but note that this list is not meant to be exhaustive.

AMINOGLYCOSIDE ANTIBIOTICS

Originally a frontline treatment for tuberculosis, aminoglycoside antibiotics also treat drug-resistant bacterial infections that do not react to penicillin-like antibiotics. Aminoglycosides are either produced by a variety of soil fungi or synthetically made from their byproducts. This family of drugs is often identifiable from the suffix "-micin" or "-mycin," depending on the type of fungi that they are synthetically made [24]. Examples of these include gentamicin, tobramycin, kanamycin, neomycin, streptomycin, and amikacin [9]. Aminoglycosides can affect hearing, balance, or both [2, 12, 14, 71]. The overall incidence is estimated at approximately 7.5% of patients [27]. The cell and molecular mechanisms of aminoglycoside ototoxicity, as well as tissue specificity, is still debated [72]. These drugs may induce apoptosis (programmed cell death), resulting in permanent damage to and oxidative stress on the system [60]. Despite reaching these tissues rapidly after being introduced into the bloodstream, they can remain present in these tissues for several days, or in some cases, weeks [72]. This lingering effect can cause changes to tissues well after the drug is administered, so monitoring the effects of these substances is performed over time.

PLATINUM-BASED CHEMOTHERAPIES

Platinum-based chemotherapy drugs are designed to bind to the DNA (genetic material) of cancer cells and prevent them from proliferating [38]. Since it was approved by the Federal Drug Administration (FDA) in the 1970s, cisplatin continues to be one of the most widely used chemotherapy products in both adults and children. It is unmatched in its effectiveness against a variety of cancers, including testicular, ovarian, cervical, osteogenic

sarcoma, and medulloblastoma [4, 58]. Despite its clinical effectiveness, it can be limited by cellular resistances and severe side-effects that can affect normal tissues. These include permanent damage to the kidneys and ears [38]. Damage to the ear is generally dose-dependent [7] and can affect both sides [48]. Cisplatin treatment results in long-term vulnerability to noise-induced hearing loss [17, 28] and can cause tinnitus [25].

A derivative of cisplatin, carboplatin, is sometimes used as an alternative [72]. Carboplatin is generally believed to be less ototoxic than cisplatin [32, 33], but is less effective at fighting cancer in some cases [42]. Oxalplatin, another platinum compound, doesn't seem to affect the hair cells as much as other platinum-based cancer drugs, but causes significant degeneration of the auditory nerve itself. How these metal compounds result in toxicity differs based how the metals are transported within the body and dispersed [18]. As side effects can vary, the pros and cons of each treatment are carefully weighed with respect to the overarching goal of stopping the cancer.

QUININE

Quinine is a common treatment for malaria. The syndrome of acute quinine toxicity is called Cinchonism (named after the Cinchona tree in South America from which quinine was isolated), and causes headache, nausea, vertigo, tinnitus, deafness, blindness, and dysphoria (generalized unhappiness, restlessness, dissatisfaction, and anxiety) [72]. Quinine often causes hearing loss in the high frequencies, and tinnitus that can be reversible if detected early in treatment [54].

NONSTEROIDAL ANTI-INFLAMATORY DRUGS (NSAIDS)

NSAIDs are some of the most widely used over-the-counter drugs in western medicine [6]. They are used as analgesic antipyretics (painkillers), anti-platelets ("blood thinners"), anti-inflammatory agents, as well as prophylactic treatment for heart attack, blood clots, and colorectal cancers [6, 11]. The most common of these drugs is salicylic acid, or aspirin, which has been long documented to cause tinnitus, reversible hearing loss, and altered sound perception. Other commonly used drugs in this family include ibuprofen and naproxen. For these drugs, with repeated doses that accumulate over time, symptoms may develop slowly and persist over a number of days. This is thought to be due to changes in blood flow [37]. In individuals without pre-existing hearing loss, high doses of NSAIDs typically cause bilateral mild to moderate hearing loss, which can be more pronounced at high frequencies. In most cases of acute NSAID ototoxicity, hearing loss recovers within 24-72 hours. Naproxen has some case reports of sudden permanent hearing loss, but in general, permanent ototoxic damage from NSAIDs is rare [72].

DRUGS KNOWN TO CAUSE OTOTOXICITY

Drug Class	Brand Name
Aminoglycoside Antibiotics	Gentamicin, Tobramycin, Kanamycin, Neomycin, Streptomycin, and Amikacin
Platinum-based Chemotherapies	Cisplatin, Carboplatin, and Oxalplatin
Quinine	Quinine-based derivatives
Nonsteroidal Anti-inflamatory Drugs (NSAIDS)	Painkillers, Blood thinners, and Anti-inflammatory agents
Loop Diuretics	Bumetanide (Bumex), Furosemide (Lasix), and Etacrynic acid (Edecrin)

LOOP DIURETICS

Loop diuretics, or drugs that affect the Loop of Henle in the kidney, modify the volume and fluid composition of the body that results in increased urine production [72]. Some common drugs in this family include bumetanide (Bumex), Furosemide (Lasix) and etacrynic acid (Edecrin) [6]. Loop diuretics are commonly used for treatment of congestive heart failure, high blood pressure, renal (kidney) failure, cirrhosis of the liver [3]. Loop diuretics can cause reversible hearing loss, which is more common when combined with aminoglycoside antibiotics [49]. This temporary ototoxicity is due to changes in blood and nutrient flow within the cochlea [19].

WORKPLACE CHEMICALS

There are a vast number of potentially ototoxic

agents that are used in a variety of industrial applications. These include chemical solvents (e.g. carbon disulfide, n-hexane, toluene, p-xylene, ethylbenzene, n-propylbenzine, sterene, methlystyrene, and trichloroethylene) asphyxiants (e.g. carbon monoxide, hydrogen cyanide, tobacco smoke), nitriles (3-butenenitrile, cis-2-pentenentrile, acrylonitrile, cis-crotonitrile, 3,3′-iminodipropionitrile) and certain metals and compounds (mercury, germanium dioxide, tin, lead, etc.). Occupational Safety and Health Administration (OSHA) and National Institute for Occupational Safety and Health (NIOSH) standards require employers to maintain exposure levels to substances beneath a Permissible Exposure Limit to prevent damage. As many of these substances are absorbed through the skin, inhaled or ingested, personal protective equipment such as gloves, arm sleeves, aprons, etc., is mandated to prevent exposure to hazardous compounds. Employers typically go to great lengths to replace hazardous chemicals with those that are less toxic or use engineering controls such as enclosures and ventilation when this is not possible. Documentation of these substances and proper protocol should be identifiable in the Safety Data Sheet logs from your employer. As an employee, you have a right to work in conditions that do not pose risks of serious harm, know which of these substances you work with, and submit an inquiry without retaliation if you believes your employer is not adhering to safety protocols [68].

RADIATION AND OTOXICITY

Ototoxicity as a byproduct of radiation is thought to be due to a number of factors [73], though there is some evidence to suggest that radiation damages the delicate blood vessels in the cochlea, which starves the system of oxygen. The effects of radiation to the ear appear to be dose-related, and can result in sensorineural hearing loss. Radiation to the ear can also cause a variety of other reactions, including: ear infection [69], excessive earwax production [57], and permanent hearing loss that is progressive with time [44]. Onset of radiation ototoxicity may occur during the radiation itself, or can be delayed several years after therapy is completed [51]. Radiation that reaches the ear tissues is often used to treat tumors within the central nervous system, as well as soft tissue cancers of the head and neck [44]. The risks of ototoxicity from radiation are increased when patients require multimodal therapies, for example, both radiation and platinum-based chemotherapy [59, 70].

HOW IS OTOXICITY DETECTED?

Ototoxic monitoring has progressed significantly over the last few decades due to technological advancements and recording mechanisms, increased scientific understanding of these drugs, and a consensus that careful management can lead to prevention of symptoms. Monitoring for ototoxic effects is more common in both clinical practice and clinical trials [9]. Despite these advancements, it remains difficult for medical professionals to categorize which patients require pre-treatment screenings for specific drug classes or how genetic predisposition may impact treatment. For these reasons, referrals are often overlooked or are not implemented.

The effects of ototoxicity may go unnoticed by patients, caretakers, and medical professionals alike. Screening before treatments is also not always feasible for patients that are in poor physical health or critical condition, and not all clinics and hospitals have specialists on staff or the equipment needed to assess for hearing and balance issues. These protocols can be time-consuming and require a rigorous follow-up schedule. However, when a proper regimen is followed, ototoxic monitoring programs can be highly successful. Ototoxic monitoring requires a coordinated effort between several individuals, including: primary care physicians, oncologists, ENT specialists, audiologists, clinical pharmacists, nursing staff, clinical support specialists, and the patient. Most protocols employ sequential monitoring over time. This allows for subsequent testing to be compared to baseline measures, early identification for changes in hearing and balance, adjustment of treatment techniques when possible, and proper rehabilitation to minimize negative effects. [26]

MONITORING FOR COCHLEOTOXICITY

As high frequency hearing is typically affected first [20, 22, 23], audiometric testing designed for ototoxic monitoring focuses on hearing at ultra-high frequencies. In a routine hearing test, hearing is assessed from 250-8000 Hz. However, the range of normal human hearing spans from 20 to 20,000 Hz. High frequency audiometry extends the clinical battery up to 20,000 Hz and is one of the most sensitive measures in ototoxic monitoring protocols. [3, 10, 21] For these frequencies, special headphones are needed that encapsulate the entire ear. Speech testing is usually included to observe changes in word understanding and determine if amplification

or hearing assistive technology would be useful in treatment.

Another measure useful in ototoxic monitoring is called otoacoustic emissions (OAEs). These are signals generated by the outer hair cells in the inner ear that are detectable with a sensitive microphone, and can be measured at high frequencies using clicks or tones. OAEs are quick to administer (taking usually less than 5 minutes to measure), do not require a behavioral response, and reflect outer hair cells status—structures commonly affected by ototoxic substances [3, 10]. OAEs are especially useful in pediatric testing where the patient will not tolerate wearing headphones.

Both of these measures rely on normal middle ear function for the stimulus to reach the inner ear as needed. Clinical utility of these measures is less effective in cases of middle ear infection, which are common in pediatric patients and immunosuppressed patients [9]. The frequency and timing of ototoxic monitoring should be dependent on the ototoxic nature of the drug being used [3] and a patient's personal risk profile [44].

MONITORING FOR VESTIBULOTOXICITY

To date there is no universally accepted guideline for vestibulotoxic monitoring. A major challenge is delineating the negative effects of ototoxic drugs from general feelings of malaise associated with immobilization in the hospital and feeling debilitated.

There is no single screening test used to identify vestibulotoxicity. However, quick bedside screening tests can shed light on functional deficits caused by ototoxic agents. These include head impulse testing, headshake testing, and dynamic visual acuity testing [26]. More intensive and in-depth laboratory analyses include: computerized dynamic posturography, rotational testing, vestibular evoked myogenic potentials, video head impulse testing, and videonystagmography. All of these tests can be useful in detecting vestibular damage [31].

In addition to these objective clinical measures and patient subjective otologic symptoms, tools such as the Dizziness Handicap Inventory (DHI) and Tinnitus Handicap Inventory (THI) are also used to measure the functional impact of symptoms on the patient's daily life [26].

EFFECTS OF OTOTOXICITY

Ototoxicity poses a threat to one's quality of life and can result in difficulty in social settings, emotional distress, and problems at work and school [56]. When effective communication is disrupted or if balance concerns arise, daily tasks can become frustrating [52]. In addition, the consequences of ototoxicity can ultimately affect one's safety. With both hearing loss and balance problems, our ability to react to alarms and emergency situations can be slowed [56]. These "invisible" conditions can lead to psychosocial health problems, depression, withdrawal, and social isolation [52]. School aged children are at risk of speech and language delay, academic learning problems, and difficulty in social situations [30].

When hearing loss is identified, there are several options to consider in terms of treatment.

Rehabilitation following ototoxicity with amplification such as hearing aids is often the starting point in management of hearing loss. Digital hearing aid technology has evolved to become more user and consumer friendly. Many offer increased programmability, customization and streaming to smartphone and other Bluetooth compatible devices. In addition to hearing aids, there are other devices such as auditory trainers, amplified telephones, audio streaming systems, and speech-to-text services that hearing aid users can tap into for improved signal to noise ratio and word understanding [8].

For patients with severe to profound hearing loss, cochlear implants may provide benefit when hearing aids are unsuccessful. These devices require surgery and are installed so that they take the place of the damaged hair cells and electrically stimulate the auditory nerve directly.

More recently, implantable devices that do not need to be worn on the ear have been developed and are gaining popularity. These can be particularly useful for pediatric candidates or users that do not like wearing the device on their ear due to their active lifestyle or for cosmetic reasons.

For vestibular impairment, an essential part of the ototoxic monitoring program includes vestibular rehabilitation. These treatment plans begin with an evaluation to determine the functional impact of ototoxicity. As vestibular loss can limit vision and mobility, there are safety concerns and activities for daily living that need to be addressed. Strength,

muscle tone, sensation of touch, gross motor skills, and coordination are addressed in an adaptive treatment plan that is based on the age and abilities of the patient.

Vestibular rehabilitation programs are designed to challenge the central nervous system and facilitate compensation, develop appropriate substitution strategies, and lessen maladaptive response patterns. The remaining sensory, motor, cognitive, and neurological systems are stimulated using adaptation exercises that will help generate new nerve activity and movement patterns. The common thread for all of these programs is movement, which is imperative to the recovery process [31]. Therapy plans are designed to reduce symptoms, with progress evaluated on an ongoing basis [15].

FUTURE DIRECTIONS

Ototoxicity and drug reactions continue to be researched. An emergent strategy that is moving from preclinical work to clinical studies is a group of compounds known as otoprotective agents. These substances are used in conjunction with ototoxic treatment to try to reduce the negative effects of exposure. Some of the current otoprotective substances gaining traction in research include antioxidants, agents that reduce the formation of free radicals and disrupt the process of apoptosis (cell death) [56]. The challenge is determining how the chemical structures of these drugs impact both efficacy and safety.

Much of the current work in otoprotectant research has been focused on animal and in-vivo laboratory studies. The underpinnings of these mechanisms are not always clear. For example, strategies that are otoprotective in one species may worsen ototoxicity in another [66]. Despite conflicting results, studies are continuing to advance, with several promising strategies on the horizon. To date, however, there are no FDA approved drugs for prevention of ototoxicity [44].

Other controversial research topics have focused on promotion of cochlear gene therapy and stem cells to help regenerate damaged tissues [47, 62]. As research on these topics continues to evolve, the current best strategy for preventing ototoxicity requires an individualized ototoxic monitoring program created with your doctors and treatment team. There is no current universal approach that will work for everyone. If you or someone you know is receiving treatment using ototoxic medications or has been exposed to these substances, it is recommended that you discuss your concerns with your doctor. If the decision is made to use these substances, it is critical that an open line of communication is maintained. If you feel any changes in hearing sensitivity, dizziness, pain, pressure, or drainage from your ears, it is recommended that you discuss these with your doctor, and consider consulting an ENT physician and audiologist as part of your treatment plan.

There is a wealth of information on various chemicals, drugs, and their side effects online. The reader is encouraged to conduct more research on any specific substances they are concerned about by visiting the websites below. If you have questions regarding any of your medicines, interactions, or side effects, it is strongly recommended that you contact your doctor or a pharmacist.

- **https://medlineplus.gov/druginformation.html**
- **http://www.vigiaccess.org/ (World Health Organization sponsored website)**
- **FDA Adverse Event Reporting System (FAERS) Public Dashboard https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/adversedrugeffects/ucm070093.htm**
- **Rxlist.com**
- **Drugs.com**

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