What is ototoxicity?

Ototoxicity is defined by Hawkins as "the tendency of certain therapeutic agents and other chemical substances to cause functional impairment and cellular degeneration of the tissues of the inner ear, and especially of the end organs and neurons of the cochlear and vestibular divisions of the eighth cranial nerve".[1] This functional impairment and cellular degeneration can lead to ringing in the ear (tinnitus), hearing loss, or balance disorders.[2] Any drug with the potential to cause toxic effects to the structures of the inner ear, including the cochlea, vestibule, semicircular canals, and otoliths, is considered ototoxic.[3] The likelihood of specific classes of medications to cause ototoxicity has been well established, with over 100 drug classes associated.

The concept of ototoxicity was first brought to the forefront of medical attention in 1944 with the discovery of streptomycin.[3] Streptomycin was successfully used as a tuberculosis treatment; however, a significant number of treated patients developed irreversible cochlear and vestibular dysfunction.

Anatomy of the Ear [4,5]

The ear is a sense organ needed for the detection of sound and for establishing balance. Structures of the ear are located in one of three areas: the outer ear, middle ear, and inner ear. Figure 1 illustrates the anatomy of the ear and its associated structures.

- **Outer ear:** external portion of the ear, consisting of the pinna, or auricle, and the ear canal.
- **Middle ear:** includes the eardrum and three tiny bones of the middle ear, ending at the round window that leads to the inner ear.
- **Inner ear:** contains both the organ of hearing (cochlea) and the organ of balance (vestibulum).
  - **Cochlea**: organ of hearing; snail-shaped structure in the inner ear
    - **Stria vascularis**: the upper portion of the outer wall of the cochlear duct; contains numerous capillary loops and small blood vessels, and produces endolymph for one of the three fluid-filled compartments of the cochlea.
  - **Vestibular Labyrinth**: organ of balance; consists of three semicircular canals and the vestibule.
    - **Semicircular canals**: three semicircular, interconnected tubes that are a component of the bony labyrinth.

Figure 1: Anatomy of the Ear

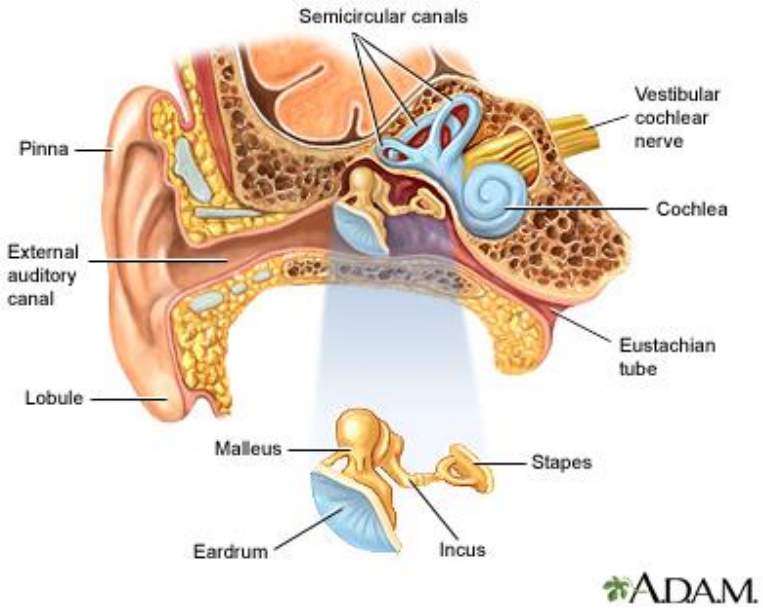

Image from: https://medlineplus.gov/ency/images/ency/fullsize/1092.jpg

CLINICAL PRESENTATION

Symptoms of ototoxicity vary considerably among different drugs and people, and can range from tinnitus to total hearing loss, and from mild imbalance to total incapacitation.[6] Symptoms may also differ depending on the location of inner ear damage (cochlea or vestibular apparatus). Cochleotoxicity is typically considered a far more serious problem because it can result in permanent hearing loss, whereas it is possible to physiologically compensate for vestibular damage. Table 1 provides a breakdown of symptoms according the location of the ear affected.

Table 1

SYMPTOMS ACCORDING TO AFFECTED LOCATION [7]	
Cochlea	**Vestibulum**
● Tinnitus (ringing in ears) ● Bilateral or unilateral hearing loss	● Vertigo ● Ataxia ● Lightheadedness ● Disequilibrium ● Nystagmus (rapid involuntary eye movements)

RISK FACTORS FOR OTOTOXICITY

There have been identified risks that correlate with an increased potential to experience ototoxicity.[8] Either age extremes, whether very young or very old, have shown to be more affected by ototoxicity compared to the age ranges in between the extremities. With an increase in daily dosage and increase in duration of therapy with ototoxic drugs, there is the increase of experiencing the adverse effects. Route of administration of the medication also has an effect on the risk for ototoxicity. Ear drops are applied directly to the ear structures resulting in the highest risk of ototoxicity followed by parenteral being less of a risk and oral administration having the least risk. Other important factors that increase the risk of experiencing ototoxicity include pregnancy, renal failure or renal transplant, hepatic dysfunction, or concomitant administration of other ototoxic drugs. Table 2 provides a summary of risk factors categorized by drug class.

Table 2

SUBSTANCE	DRUG CLASS RISK FACTORS [8] *In these conditions, drugs may be ototoxic even when given in normal clinical doses:*
Aminoglycosides	● Pregnancy ● Renal dysfunction ● Synergy with loop diuretics ● Genetic/familial predisposition *Caution: in infants and elderly, and those with a family history of ototoxic hearing loss; some may produce significant vestibular damage with normal dosing*
Diuretics	Potentiate ototoxic drugs and may also be ototoxic on their own *Caution: when used with aminoglycosides*
Salicylates	● Mildly ototoxic ● Reversible hearing impairment *Caution: watch for idiosyncratic reactions; not for use in children <18 years of age*
Quinines	● Reversible hearing impairment ● Infants ● Elderly
Antineoplastic Agents	● Higher doses and increasing number of cycles ● Cranial irradiation (current or past) ● Very young and Elderly ● Dehydration ● Renal Failure
Macrolides	Risk factors that predispose patients to macrolide ototoxicity: ● Renal impairment or a renal transplant ● Hepatic dysfunction ● Advanced age ● Gender (females at higher risk)

MECHANISMS OF DRUG-INDUCED OTOTOXICITY

Ototoxic medications generally exert their effects on primarily one portion of the ear. Damage is caused by either direct action of the agent on the hair cells (of the cochlea or vestibulum) or by affecting the stria vascularis, resulting in degeneration of their supporting cells.[8] This destruction can be stopped at

any stage by removing the toxic agent, and may or may not result in recovery of hearing and balance. The degree of reversibility is usually related to the agent and dose used. The most prevalent causative agents, aminoglycosides, typically result in permanent damage, which occurs in two stages: (1) biochemical damage followed by (2) cell death.

MEDICATIONS THAT CAUSE OTOTOXICITY

There are more than 200 known ototoxic medications (prescription and over-the-counter) on the market today.[2] Those most commonly referred to in the literature are: salicylates, quinine, aminoglycosides, macrolides, loop diuretics, and antineoplastic agents. Table 3 provides a summary of ototoxic drugs information on a representative agent from each class.

Aminoglycoside (oral):

- **Background:** The aminoglycosides are a class of antibiotics which include streptomycin, neomycin, amikacin, gentamicin tobramycin, and others, with neomycin being the only oral aminoglycoside available.[9] Aminoglycosides are most commonly used to treat serious gram-negative infections in combination with □-lactam antibiotics, to treat gram-positive endocarditis in combination with □-lactam antibiotics or vancomycin, and to treat tuberculosis.[3] Aminoglycosides work by binding to the bacterial 30S ribosomal subunit and preventing bacterial protein synthesis. Aminoglycosides exhibit bactericidal activity, concentration-dependent killing, and have a significant post-antibiotic effect. Aminoglycosides are the most vestibulotoxic of the ototoxic drugs.
- **Prevalence:** Antibiotics in some countries are freely prescribed, in these countries aminoglycosides cause up to 66% of medication induced deafness.[3] As a result of the agent and dosing up to 33% of adult patients on an aminoglycoside may experience audiometric changes. The incidence is decreasing due to improvements in monitoring and heightened awareness.
- **Mechanism of ototoxicity:** Aminoglycosides produce cochlear toxicity that results in the hearing loss of high frequencies and the destruction of hair cells.[10] Aminoglycosides can cause both reversible and irreversible impairment of cellular function. Reversible impairment is believed to occur from the competitive blockade of calcium channels required for the generation of receptor or action potentials. Irreversible impairment occurs when aminoglycoside uptake into hair cells results in cell death from apoptosis and possibly cellular necrosis mechanisms by disruption of mitochondrial protein synthesis and the formation of free radicals. Aminoglycosides may persist in inner ear fluids for months after treatment, which may account for delayed hair cell death after cessation of treatment. Neomycin, one of the more cochleotoxic aminoglycosides when dispensed orally, is not frequently recommended for systemic administration.[3] It is among the slowest aminoglycosides to be cleared, therefore possibly delaying toxicity and recovery.
- **Prevention:** Aminoglycoside toxicity may be prevented by identifying high risk patients and selecting alternative antibiotics.[3] Patients should also avoid noisy and loud environments for at least 6 months after therapy. During this time patients are more susceptible to noise-induced cochlear damage.

Loop diuretics:

- **Background**: The loops are a class of diuretics that include furosemide, torsemide, bumetanide, and ethacrynic acid.[11] Loops are most commonly used to treat congestive heart failure, renal failure, cirrhosis, and hypertension. They target proteins that mediate the transfer and balance of ions across cell membranes found in many epithelial and nonepithelial cells, including the stria vascularis of the cochlea. Inhibiting these proteins alters ion excretion within the stria vascularis, resulting in cell shrinkage or swelling, and extracellular edema.
- **Prevalence:** It is estimated that ototoxicity occurs in 6-7% of patients taking loop diuretics.[3] Occurrence of loop diuretic ototoxicity is dependent upon several factors, including dose, history of renal failure, and co-administration of other ototoxic agents.
- **Mechanism of ototoxicity:** The ototoxic effects of loop diuretics are primarily associated with the stria vascularis, where changes in the ionic gradients between fluids of the inner ear results in endothelial edema. Ethacrynic acid-induced ototoxicity typically develops more gradually.[3]
- **Prevention:** Loop diuretic-induced ototoxicity may be prevented by using the lowest effective dose and assessing risk factors such as co-administration of other ototoxic agents and history of renal failure.[3] Due to the well-

documented potentiation and synergism of ototoxic effects of loops and aminoglycosides, co-prescription of these drugs is not recommended.

Salicylates:

- **Background**: Salicylates are nonsteroidal anti-inflammatory drugs that are most commonly used for the symptomatic relief of mild to moderate pain and fever reduction due to their analgesic and anti-inflammatory effects.[9] Aspirin is the most commonly used salicylate and the only of its class used for arterial thrombosis prevention due to its antiplatelet effect. Aspirin works by irreversibly inhibiting cyclooxygenase (COX) 1 and 2 enzymes resulting in decreased formation of prostaglandin precursors ultimately inhibiting platelet aggregation along its anti-inflammatory, antipyretic, and analgesic properties.
- **Prevalence:** Salicylate-induced ototoxicity has been reported at an incidence as high as 1% and is most commonly observed in elderly patients, even at low doses.[3]
- **Mechanism of ototoxicity:** The mechanism of salicylate ototoxicity is multifactorial, but seems to involve metabolic rather than morphologic changes within the cochlea.[3] Salicylic acid quickly penetrates the cochlea, resulting in perilymph levels parallel to serum levels. Increasing perilymph levels leads to tinnitus and generally a reversible flat sensorineural hearing loss. Recovery usually occurs 24-72 hours after discontinuation of the drug.
- **Prevention:** Salicylate toxicity may be prevented by using the lowest effective dose, or using an appropriate non-salicylate alternative.[3] Assessment of risk factors such as age (elderly or less than 18 years old) or concomitant administration of other ototoxic agents should also be performed.

Quinine:

- **Background**: Quinine is an alkaloid derived from the bark of cinchona tree that has been used in the treatment of malaria and as an antipyretic since the early 1600s.[10] Presently, intravenous quinine is approved for the treatment of chloroquine resistant malaria due to strains of *Plasmodium falciparum*. Quinine works by elevating the pH of parasitic acid vesicle and upsets molecular transport phospholipase activity.[9] For a therapeutic effect, a plasma concentration of 10 mg/L is recommended. However, plasma quinine concentrations above 5 mg/L in malaria patients can become ototoxic, selectively affecting high-frequency hearing.
- **Prevalence:** Clinical auditory toxicity from quinine has been reported sparingly in malaria patients, despite quinine concentrations likely exceeding 10 mg/L.[10] This is probably contributed to differences in protein binding, the free fraction of quinine being reduced by 25% in patients with uncomplicated malaria and up to 40% for severe malaria. Healthy volunteers were noted to have only one-third of the concentration of the main plasma binding protein for quinine found in malaria patients.
- **Mechanism of ototoxicity:** Quinine ototoxicity, or cinchonism (the accumulation of cinchona alkaloids) is known to produce reversible hearing loss and tinnitus, similar to salicylates.[10] Outer hair cells of the cochlea seem to be the common site for the ototoxic effect of both drugs; quinine exposure interrupts the hair cell's' membrane potential. Quinine-induced vasoconstriction and subsequent reduction of cochlear blood flow has been postulated as another explanation for ototoxicity. Transient hearing loss is the first manifestation of quinine ototoxicity, and occurs a few hours after initiating high-dose therapy (up to 2 g in the treatment of malaria). After prolonged daily dosing (200-300 mg), up to 20% of patients might have some degree of hearing loss. Hearing loss is typically reversible with bilateral symmetric sensorineural hearing loss that affects higher frequencies initially (at 4, 6 and 8 kHz). However, permanent hearing loss has also been reported, affecting the conversational frequencies.
- **Prevention:** To prevent irreversible hearing loss, ultrahigh-frequency audiometry (10-20 kHz) has been advocated for accurate monitoring of impending cinchonism.[10] Some studies suggest that quinine-induced tinnitus can be prevented with nimodipine, a calcium channel blocker, in a dose-dependent manner. However, the calcium channel blocker verapamil did not prevent hearing loss after quinine administration to guinea pigs.

Antineoplastic agents:

- **Background:** The most common antineoplastic agents associated with ototoxicity are the platinum-based compounds, cisplatin, and to a lesser degree, carboplatin.[3] These agents are cell-cycle nonspecific alkylating agents that result in DNA replication disruption.
- **Prevalence:** Prevalence increases with dose, duration, and number of cycles along with renal function and concurrent administration of other ototoxic agents.[11] The pediatric population has historically shown to have a higher incidence and severity of hearing loss. As many as 61% of pediatric patients receiving the platinum-based antineoplastic agents experience ototoxic effects.
- **Mechanism of ototoxicity:** Free-radical production and cell death are the two components of ototoxicity brought on by platinum containing agents that can ultimately lead to irreversible hearing loss.[11] After cisplatin exposure, free radical species are produced in the inner hair cells that result in mitochondria-mediated and caspase-mediated apoptotic cell death resulting in loss of hearing.
- **Prevention:** Baseline audiograms for each cycle and periodic follow-up audiograms are recommended to assess efficacy of drug cycle while monitoring for ototoxic effects.[12] Due to potential of extended drug retention, it is also recommended to continue audiometric testing for several years after completion of therapy. Duration of long term post therapy testing is patient specific and should be determined using best clinical judgement. Patients should take caution to avoid excessive noise for up to six months following therapy.

Macrolides:

- **Background:** The macrolides are a class of antibiotics which include azithromycin, clarithromycin, erythromycin, and fidaxomicin. These antibiotics are bacteriostatic agents that act by binding to the 50S ribosomal subunit of susceptible organisms, therefore inhibiting bacterial protein synthesis.[13] Erythromycin is considered the substitute of choice in group A streptococcal and pneumococcal infections in penicillin-sensitive patients.[3] Erythromycin is the antibiotic of choice for *Legionella* pneumonia and other atypical pneumonias. Azithromycin and clarithromycin are newer macrolide antibiotics with widespread clinical use due to fewer gastrointestinal side effects and a broader antimicrobial spectrum than erythromycin.
- **Prevalence:** The first reports of erythromycin-induced ototoxicity were reported in 1973, when two women developed reversible hearing loss following treatment for pneumonia with intravenous erythromycin.[10] In 1975, an additional case of reversible hearing loss was reported, this time with oral erythromycin. Further reports of reversible hearing loss soon followed, including complaints of vertigo in addition to tinnitus and hearing loss, indicating a possible vestibulotoxic as well as cochleotoxic effect. Irreversible ototoxicity findings were first documented in 1986 when a patient experienced hearing loss and tinnitus after four doses of intravenous erythromycin. After 1 year, her audiogram slightly improved from 65 dB to 45 dB at 8 kHz, but tinnitus persisted. Further case reports of reversible and irreversible hearing loss with erythromycin have been published, and more recently with the newer macrolides, azithromycin and clarithromycin.
- **Mechanism of ototoxicity:** The mechanism of ototoxicity for the macrolides is not fully understood, but animal studies suggest cochleotoxicity as well as ion transport impairment within the stria vascularis, resulting in endothelial edema.[3] Onset is typically within 3 days of initiation of treatment, with speech frequencies affected more than higher frequencies. Ototoxic effects of macrolides are usually reversible.
- **Prevention:** Patients who experience macrolide-induced ototoxicity generally tend to have other risk factors present such as advanced age, renal impairment or transplant, hepatic dysfunction, doses of more than four grams per day, and intravenous administration, and gender (females are at a higher risk).[14]

Table 3: COMMON OTOTOXIC DRUGS [9, 13]						
Class	**Loop Diuretic**	**Aminoglycoside**	**Salicylate**	**Quinine**	**Antineoplastic**	**Macrolide**
Generic	**Furosemide**	**Neomycin**	**Aspirin**	**Quinine**	**Cisplatin**	**Erythromycin**
Brand	Lasix®	Neo-Fradin®	Ecotrin®	Qualaquin®	Platinol®	Ery-Tab®
FDA Approval	1966	1952	1939	2005	1978	1952
How Supplied	Oral (tablet, liquid) Intravenous Intramuscular	Oral (tablet) Topical	Oral (tablet) Rectal	Oral (tablet, capsule)	Solution for injection	Oral (tablet, capsule) Topical (gel, pad, solution)
Dosage	20-80 mg PO Daily	4-12 g PO Daily in divided doses	81 mg PO Daily	648 mg PO Q 8 hours for 7 days	50-70 mg/m^2 IV as a single dose Q 3-4 weeks	250 mg PO Q 6 hours
Pregnancy Category	C	B	Avoid use, especially during the 3rd trimester	C	D	B

STRATEGIES FOR PREVENTION AND CONTROL

Basic Management Strategies

Currently, there are no treatments to reverse drug-induced hearing loss, apart from withdrawing the offending agent as soon as toxicity is suspected.[7] Therefore, the importance of preventing adverse effects secondary to ototoxic drugs must be emphasized. Prevention may be accomplished by either avoiding or discontinuing the ototoxic agent (if an appropriate alternative is available).

There are presently no FDA-approved drugs specifically for tinnitus, and no medications have been shown to resolve the cause of tinnitus.[15] However, there are some drugs that may provide relief of some severe tinnitus symptoms. Medications most often used in tinnitus management are psychoactive drugs that treat behavioral issues secondary to tinnitus (such as stress, anxiety, and depression). Because there is a cyclic relationship between negative emotions and tinnitus (tinnitus causes anxiety, which in turn exacerbates tinnitus and causes more anxiety), it is possible that psychoactive drugs may make tinnitus less noticeable for some patients. The dosing for these medications is the same as typical dosing for their respective indications. Research shows very limited efficacy in patients without anxiety, depression, or obsessive compulsive disorder. Furthermore, some research suggests antidepressants and antianxiety medications may reduce neural plasticity and make it more difficult for patients to naturally accommodate tinnitus over time. Table 4 summarizes common antidepressants and antianxiety medications used in the treatment of tinnitus.

A number of over-the-counter substances (pills, powders, herbs, drops, etc.) are marketed as "tinnitus remedies".[7] Examples include Ring Relief®, Ring STOP®, TinniFree®, and Similasan Ear Relief®. There is no reliable scientific evidence that these homeopathic products (or their ingredients) have any

impact on tinnitus. While there may be anecdotal success stories related to these products, any reported benefits are likely due to a temporary placebo effect. Patients should beware of these products as they are not regulated by the FDA and have no scientific measurable effect.[15] It is important to educate the patient on avoiding treatment to alleviate symptoms of ototoxic drugs rather than discontinuing the causative agent. By only treating the symptoms and not removing the ototoxic agent, the patient is at a risk of increasing the severity of hearing damage that could ultimately be irreversible.

Table 4

Common Drugs Used in Relation to Tinnitus [15]	
Antidepressants	Anxiolytics
● Clomipramine (Anafranil®) ● Desipramine (Norpramin®) ● Imipramine (Tofranil®) ● Nortriptyline (Pamelor®) ● Protriptyline (Vivactil®)	● Alprazolam (Xanax®) ● Clonazepam (Klonopin®) ● Diazepam (Valium®) ● Lorazepam (Ativan®)

Monitoring

Audiologic monitoring for ototoxicity is primarily performed for two reasons: (1) early detection of hearing status changes presumed to be attributed to a drug so that changes in the drug regimen may be considered, and (2) audiologic intervention when hearing impairment has occurred.[16]

Three main approaches to audiologic monitoring have emerged over the past decades: the basic audiologic assessment, high-frequency audiometry (HFA), and otoacoustic emission (OAE) measurement. Each approach varies in utility, reliability, purpose, and applicability to specific patient populations, and may be used separately or in combination.

Ototoxicity monitoring tests require a baseline evaluation, ideally performed prior to any drug administration so that future results have a clear basis for interpretation.[16] Due to the high incidence of pre-existing hearing loss in the population, especially the elderly, lack of pre-treatment baseline evaluation makes establishing an association between the drug and a drug-induced hearing loss substantially more difficult. If changes occur on subsequent follow-up testing, further testing is warranted to determine if the changes are secondary to the drug or other factors, such as otitis media. Baseline testing should be relatively comprehensive and include pure tone thresholds in the conventional frequency range, HFA, tympanometry, speech audiometry, and testing of OAEs.

Basic audiologic assessment continues to be an important aspect of ototoxicity monitoring.[16] However, basic audiologic assessment is conventionally only conducted up to 8 kHz (normal hearing range), and most damage from ototoxic agents begins with impairment of hearing at the highest frequencies first, and progresses to lower frequencies as the exposure continues. Thus, most early cases of drug-induced hearing loss are not recognized via standard audiometric testing. It is essential to the follow-up if a change in hearing occurs to determine the patient's ability to hear speech for normal communication. It is also the cornerstone of differential diagnosis, particularly to rule-out incidental conductive involvements (e.g. otitis media) and to assess the range of hearing relative to speech communication.

Although less conventional tests, HFA and OAE testing have become well established for ototoxicity monitoring, and are more likely to be used at the first level of monitoring patients treated with potentially ototoxic medications.[16] These exams are used first because of their sensitivity and ability to detect changes in the auditory system earlier than may be possible with other examination.

The earliest effects of ototoxic drugs are commonly manifested by the outer hair cells (OHCs) of the basal cochlear turn.[16] HFA comprises air-conduction threshold testing for the frequencies above 8 kHz, allowing the detection of aminoglycoside-induced or cisplatin-induced ototoxicity long before changes may be detected in the conventional range. HFA may not be used in all patients, such as those with hearing loss in the conventional frequency who may not have measurable hearing at high frequencies.

OAEs are generated by the outer hair cells in the cochlea in response to an auditory stimulus delivered to the ear. The emissions are measured by a small probe inserted in the ear canal.[17] The most commonly used OAEs are transient OAEs (TEOAEs) or distortion product OAEs (DPOAEs).[16] TEOAE responses typically change before hearing threshold in the conventional range, but not before changes in

the HFA thresholds. Testing DPOAEs may detect ototoxic change earlier than TEOAEs, likely due to the fact that DPOAEs can be measured at higher frequencies, and thus are more sensitive to the cochlear frequencies first affected.

Both HFA and OAE testing are problematic in patients with prior hearing loss, particularly the elderly, because there may be limited or no responses due to pre-existing losses of OHCs in the cochlear basal region.[16] HFA usually detects ototoxic change earlier than DPOAEs, and is less affected by otitis media than OAEs.

Grades of Ototoxicity

To determine the interval of change in ototoxic effects, the most commonly used criteria was published in 1994 by the American Speech-Language-Hearing Association (ASHA).[16] Changes in hearing are compared against baseline measures, and retesting must be completed within 24 hours to confirm results. The following criteria have shown to be accurate in detecting ototoxic change without yielding false findings.

One of the following must be met to identify significant ototoxic change:

- 20 dB or greater decrease in pure-tone threshold at one frequency
  - 20 dB is equivalent to a whisper or rustling leaves [18]
- 10 dB or greater decrease at 2 adjacent frequencies
  - 10 dB is equivalent to breathing [18]
- Or loss of response at 3 consecutive test frequencies

Although the FDA has not established Good Clinical Practices for grading adverse events in hearing, the two most commonly used adverse event scales for hearing are the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Ototoxicity Grades and Brock's Hearing Loss Grades. Refer to Table 5 for the ototoxicity grades determined by the CTCAE.

Table 5

CTCAE Ototoxicity Grades [16]		
Population	**Children**	**Adults**
Grade 1	Loss of 15-25 dB relative to baseline, averaged at 2 or more contiguous frequencies in at least one ear	
Grade 2	Loss of >25-90 dB, averaged at two contiguous test frequencies in at least one ear	
Grade 3	Hearing loss warranting therapeutic intervention, including hearing aids (e.g. >20 dB bilateral hearing loss in the speech frequencies; >30 dB unilateral hearing loss; and requiring additional speech language related services)	Loss of >25-90 dB, averaged at three contiguous test frequencies in at least one ear
Grade 4	Indication for cochlear implant and requiring additional speech language related services	Profound bilateral hearing loss >90 dB hearing loss

The Brock's Hearing Loss Grade test was originally designed to determine platinum-induced ototoxicity. The grades of hearing loss are assigned based on the standard pure-tone audiologic frequencies at which hearing thresholds equal or exceed 40 dB hearing loss.

Table 6

Grade 0	Hearing thresholds <40 dB at all frequencies
Grade 1	Thresholds 40 dB or greater at 8 kHz
Grade 2	Thresholds 40 dB or greater at 4-8 kHz
Grade 3	Thresholds 40 dB or greater at 2-8 kHz
Grade 4	Thresholds 40 dB or greater at 1-8 kHz

Professional Education

A large percentage of drug-induced hearing impairment results from the inappropriate use of ototoxic medications by multipurpose health care providers (HCP).[8] The importance of audiometric testing should be emphasized in patients: (1) at risk following long-term treatment with ototoxic medications; (2) not at risk during therapy with agents that can exacerbate the ototoxic effect of other drugs.

Strategies for Communicating with Persons with Hearing Loss [19]

There are effective ways to communicate with a person with hearing loss without coming across as rude or unsympathetic. Following are a few examples of how to communication can be improved:

- Speak at close range (within 3 feet)
- Speak slowly and distinctly
- Maintain good eye contact
- Reduce or eliminate background noise
- Ask for repetition to insure understanding

Example Tinnitus Screening [19]

Table 7 is a set example of questions pharmacists may use to identify and diagnosis tinnitus, or ringing in the ears.

Table 7

Questions for Tinnitus Identification		
Is the tinnitus in only one ear, or louder in the ear?	Yes	No
Does the tinnitus keep you from sleeping?	Yes	No
Does the tinnitus affect your ability to concentrate?	Yes	No
Do you want to see someone for help with your tinnitus?	Yes	No

Public Education

Insufficient public education on ototoxicity and the lack of general knowledge regarding the risk of ototoxic damage are both hurdles to successful prevention.[8] The aim of public education should be the provision of information to enable individuals to use medications appropriately. Public information should increase awareness about the risks from improper use or abuse of ototoxic drugs, particularly related to dosage and duration of their administration. General information about the potential interaction of two concomitant ototoxic medications would also be useful in the prevention of their additive or synergistic effects. Suggested educational materials include posters and brochures, preferably produced in collaboration with interested non-governmental organizations (NGOs). Posters should be used in pharmacies, health centers, hospitals, schools, and other suitable public places.

Patient Education

The patient should avoid significant noise exposure during and for several months after taking an ototoxic drug.[19] Patients with hearing aids should ensure that their power output is carefully monitored to avoid any noise damage. Patients should inform their physician of any changes to hearing, balance, or tinnitus.

The Future

Although there are currently no FDA approved drugs to prevent or treat ototoxin-induced hearing loss, researchers have been investigating D-methionine (D-met) as an otoprotective agent for the past decade.[20] D-met is the optical isomer of the essential amino acid L-methionine, and is believed to be one of the most promising otoprotective agents at this time. The otoprotective action of D-met has been documented in a variety of species (not human) against cisplatin, carboplatin, and aminoglycosides. D-met may have multiple protective actions, but likely primarily works as both a direct and indirect antioxidant. Unlike many amino acids, methionine is reversibly oxidized and can serve as a free radical scavenger, binding to the free radicals produced by aminoglycosides and cisplatin, and inhibiting their ototoxic effect. Studies conducted by Campbell et al. reported efficacy in the use of several animal species.[20] In an experiment comparing the efficacy of injected and orally administered D-met in rodents, oral administration was equally effective. An orally administered dose of 1000mg/kg 2 hours before an infusion of 16mg/kg cisplatin proved to be as efficacious as injected D-met. Although D-met's efficacy has been established in animals, it has not been investigated in humans, therefore no specific dose can be recommended at this time.

OTHER RESOURCES [21]

Table 8 is a compilation of contact information for various audiology clinics throughout the state of Alabama which can be used if a patient has suspected ototoxicity and requires a referral for audiometric evaluation.

Table 8

AUDIOLOGY CLINICS IN ALABAMA [21]			
Clinic	**Location**	**Phone**	**Contacts/email if applicable**
Auburn University Speech and Hearing Clinic	Auburn, AL	(334) 844-9600	• Marsha Kluesing, Au.D., CCC-A • Kelli Watts, Au.D., CCC-A • Martha Wilder Wilson, Au.D., CCC-A
ENT Associates of Alabama	Montgomery, AL	(334) 272-8644	• J. Noble Anderson, Jr., M.D., FACS
Hoover ENT Audiology	Hoover, AL	(205) 733-9595	• Suzanne Baggett, Au.D. • Leigh Burnett, Au.D., CCC-A, FAAA
Ascent Audiology & Hearing	Tuscaloosa, AL	(205) 523-8199	• Keith Eargle, Au.D., CCC-A • Christie H. Burch, Au.D., CCC-A, FAAA • info@ascentaudiologytuscaloosa.com
Birmingham Speech and Hearing Associates	Birmingham, AL	(205) 871-3878	• Jill Byrd, CCC-A • Leslie Crawford, Au.D. • Cynthia Serota, Au.D.
Hearing Associates of Dothan	Dothan, AL	(334) 702-4327	• Jamie Shumaker, Au.D., CCC-A
Bay Audiology Services, Inc.	Mobile, AL	(215) 689-3241	• Pam Dyas Vautier, M.S.C., CCC-A
Alabama Hearing and Balance Associates	Foley, AL	(251) 970-3277	• Elizabeth Roberts, Au.D. • Richard Roberts, Ph.D. • info@hearingandbalance.net
Shoals Hearing Clinic, P.C.	Florence, AL	(256) 740-8383	• Marilyn Gresham, Au.D. • Richard Gresham, Au.D. • shoalshearing@aol.com

CONCLUSION

Therapeutic agents and other chemical substances can cause functional impairment and cellular degeneration of tissues in the inner ear, known as ototoxicity. This functional impairment can lead to ringing in the ear, hearing loss or balance disorders as a result of the administration of ototoxic drugs. Drug-induced ototoxicity can be caused by aminoglycosides, loop diuretics, salicylates, macrolides, antineoplastic agents, quinine and various other agents. These medications exert their effect by causing damage to the hair cells or by affecting the stria vascularis. The effect of ototoxic drugs is stopped by the removal of the toxic agent. Because there are no current treatments to reverse drug-induced ototoxicity, prevention strategies are of the utmost importance. Monitoring for ototoxicity has become a mainstay in preventing impairment with these medications. Early detection of hearing status changes necessitates alternative therapy to prevent possible irreversible damage in the future. Lack of knowledge among patients and healthcare providers regarding ototoxicity is a main obstacle for prevention. Therefore, the education of the public, patients, and medical professionals on ototoxicity awareness is vital in minimizing the occurrence.

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