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Pharmacological Ototoxicity: Pathophysiology, Clinical Impact, and Current Preventive Options

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ABSTRACT

Introduction: Ototoxicity, involving damage to the cochlear and vestibular structures of the inner ear, is a complication of pharmacotherapy. Hearing loss and balance disorders caused by medications are of particular clinical significance because they significantly impair the quality of life in adults and speech development in children. *Objective*: We aim to summarize current knowledge on ototoxic drugs and hearing protection strategies. *Material and methods*: We reviewed the scientific literature published from 2004 to mid-2025. *Results*: The main groups of ototoxic drugs include aminoglycosides, loop diuretics, platinum-based compounds, salicylates/ Non-steroidal anti-inflammatory drugs (NSAIDs), antimalarial agents, and immunotherapies. Ototoxicity is often irreversible, especially with aminoglycosides and platinum compounds. This information is critical in children and in patients treated for drug-resistant tuberculosis, because the risk may be increased and the effects can be long-lasting. To minimize irreversible damage, primary otoprotection efforts focus on reducing exposure and on early detection of warning signs. Methods include modifying dose schedules and preserving renal function to prevent drug accumulation. Patients should limit their noise exposure and have regular audiological examinations. Sodium thiosulfate is currently the only otoprotective drug with strong clinical data and is approved in selected pediatric indications. It is administered after cisplatin, with a delay, to reduce ototoxicity while preserving the antitumor effect. *Conclusions*: It is essential to apply otoprotective strategies consistently. Sodium thiosulfate may be considered in selected patients. Research into new otoprotective agents should be continued.

Keywords: ototoxicity; drug-induced hearing loss; cisplatin; aminoglycosides; otoprotection

1. INTRODUCTION

Ototoxicity is damage to the inner ear or the vestibulocochlear nerve caused by exposure to certain drugs or chemicals. It includes both cochleotoxicity (primarily sensorineural hearing loss and tinnitus resulting from cochlear damage) and

vestibulotoxicity (balance disorders and vertigo resulting from vestibular organ damage) (Józefowicz-Korczyńska et al., 2021; Cianfrone et al., 2011). The consequences of ototoxicity might be reversible and temporary, as observed in high doses of salicylates, some NSAIDs, or antimalarial compounds, or irreversible and permanent, such as in aminoglycosides or platinum compounds (Józefowicz-Korczyńska et al., 2021; Cianfrone et al., 2011; Dillard et al., 2022; Lindeborg et al., 2022).

Ototoxicity is a spurring public health problem. It is further projected that platinum-based chemotherapy could lead to several hundred thousand new cases worldwide each year. ototoxicity new diagnosed cases aminoglycoside-induced tens of the same (Dillard et al., 2022; Lindeborg et al., 2022). Furthermore, short-term aminoglycoside treatments worldwide result in tens of thousands of cases of ototoxic hearing loss each year (Lindeborg et al., 2022). Current studies link treatment-induced hearing loss not only to a reduced quality of life (communication problems, social isolation, occupational difficulties) but also to cognitive impairment and depression in adults (Cianfrone et al., 2011; Lindeborg et al., 2022; Lee et al., 2024).

This is particularly problematic for pediatric patients. Hearing dysfunctions strictly linked to cisplatin therapy affect up to 50-70% of children, and they are commonly irreversible. It initially affects high frequencies before reaching the speech frequencies (Dillard et al., 2022; Romano et al., 2020). Even early and moderate hearing loss can significantly impact a patient's speech and language development. This process can hinder functioning at school and in society. It leads to long-term limitations in educational and professional potential.

Among the classic classes of drugs that hurt the cochlea are aminoglycosides, platinum-based agents, loop diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), and antimalarials (Józefowicz-Korczyńska et al., 2021; Cianfrone et al., 2011; Lindeborg et al., 2022). Aminoglycosides can cause irreversible damage to the cochlear or vestibular nerve. Medicine classifies platinum-based drugs as ototoxins. Some studies have reported permanent hearing loss in 60–80% of cases, especially among children and older people.

Loop diuretics frequently trigger short-term, reversible hearing loss and tinnitus (e.g., furosemide or bumetanide) as well as high doses of salicylates/NSAIDs (salicylic acid, ibuprofen, naproxen). Permanent: Continuous exposure to a mixture of other ototoxins can lead to permanent injury (Cianfrone et al., 2011; Lindeborg et al., 2022). Antimalarial medications (quinine and chloroquine) also cause reversible hearing and balance disorders, especially with long-term use (Józefowicz-Korczyńska et al., 2021). More recently, new ototoxic drugs have come to attention. These are, among others, some targeted treatments (that is, tyrosine kinase inhibitors), immune checkpoint blockers, and new generation chemotherapy and antiretroviral drugs whose potential ototoxicity cases have recently been more often described in the literature (Józefowicz-Korczyńska et al., 2021; Lindeborg et al., 2022; Lee et al., 2024; Bonilla et al., 2025)

The spectrum of ototoxic drugs is broad, and the high frequency of use in everyday clinical practice, combined with severe, often irreversible consequences for hearing and balance, justifies the need for systematic monitoring. Particularly in the most vulnerable populations, early detection and the development of otoprotective strategies are essential, as discussed in this paper.

Purpose of the study and research questions

This review aims to present the current knowledge on ototoxic drugs and both pharmacological and non-pharmacological otoprotective strategies, with an emphasis on their clinical significance and clinical implementation. Accordingly, the review addresses the following research questions:

1. Which drug classes most commonly cause irreversible hearing loss and/or balance disorders?
2. What are the key cellular and molecular mechanisms underlying the ototoxicity of specific drug groups?
3. Which otoprotective strategies - pharmacological and non-pharmacological - are currently supported by the strongest clinical evidence, and where do significant knowledge gaps persist that require further research?

2. REVIEW METHODS

We conducted the primary search in PubMed and supplemented it with results from Google Scholar and Scopus. The search covered the last 15-20 years (from around 2004 to mid-2025), with the possibility of including older, classic publications if they were relevant to describing the pathophysiology of ototoxicity or otoprotection. We restricted the literature analysis to English-language publications and, when available, Polish-language review articles and guidelines. The search used combinations of keywords in English, combined with logical operators (AND/OR), for example:

- Ototoxicity, drug-induced hearing loss, cochleotoxicity, vestibulotoxicity, otoprotection, otoprotective agents
- In combination with drug classes and specific substances:
- aminoglycosides, gentamicin, amikacin, tobramycin

- cisplatin, carboplatin, platinum-based chemotherapy
- loop diuretics, furosemide, bumetanide
- salicylates, NSAIDs, aspirin
- antimalarial drugs, quinine, chloroquine, hydroxychloroquine
- tyrosine kinase inhibitors, immune checkpoint inhibitors, immunotherapy
- and, for pediatric literature, terms such as child, children, pediatric, and paediatric.

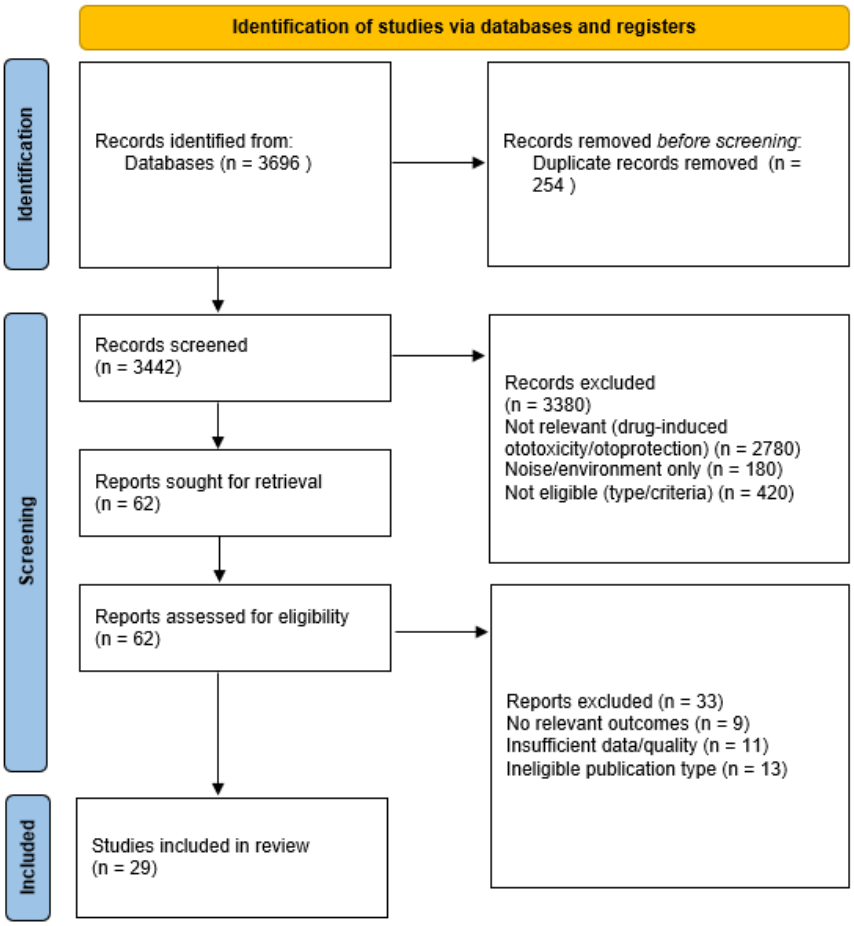

Figure 1. PRISMA 2020 flow diagram of study identification and selection. Of 3,696 records identified, 254 duplicates were removed, leaving 3,442 records screened. After title/abstract screening, 3,380 records were excluded and 62 full-text reports were assessed; 33 were excluded, resulting in 29 studies included in the final synthesis.

The inclusion criteria were as follows:

- original articles, reviews, meta-analyses, and guidelines concerning drug-induced ototoxicity and/or otoprotection;
- studies involving adults and children (allowing for the distinction of pediatric-specific data, especially about cisplatin and aminoglycosides);
- Clinical and observational studies (cohort, cross-sectional, case-control), as well as experimental studies (in vitro, in vivo), provided they offered relevant insights into the cellular and molecular mechanisms of ototoxicity or potential otoprotective strategies.

Exclusion criteria included:

- isolated case reports, except those concerning a rare drug or a new class of potentially ototoxic therapy;
- articles without full-text access;
- Studies in which the predominant exposure was noise, acoustic trauma, or other factors unrelated to pharmacotherapy (e.g., exclusively environmental ototoxicity), unless they significantly analyzed drug interactions;

- Publications that failed to meet quality criteria (e.g., insufficient data, lack of information on drug exposure, lack of definition of hearing/balance endpoints).

First, we conducted a preliminary selection based on titles and abstracts, followed by a review of the full texts of the publications. In case of doubt regarding eligibility, we considered the article's mechanistic or clinical relevance to the central questions of the review (groups of ototoxic drugs, mechanisms of damage, otoprotective strategies). Figure 1 (PRISMA diagram) shows the study selection process.

3. RESULTS & DISCUSSION

3.1. Mechanisms of inner ear damage caused by drugs

3.1.1. Vulnerability of the cochlea to damage

The inner ear is particularly susceptible to ototoxicity; this is in large part due to its exceptional architecture and the metabolic energy it takes to sense sound. The organ of Corti in the cochlea that serves inner and outer hair cells. These cells are critical for converting the mechanical pressure of sound waves into neural impulses. The spiral ganglion neurons then relay these. The lateral wall, formed by the stria vascularis, controls the endolymph ionic composition and produces endolymphatic potential. This process is the key to how mechanoelectrical transduction (MET) channel located at the tips of hair-cell stereocilia operate (Kamogashira et al., 2015)

Situations that can lead to permanent hearing loss include damage to hair cells, supporting cells, the stria vascularis, or the cochlear microcirculation.

3.1.2. Common mechanisms of ototoxic drugs

There is evidence of standard mechanisms of damage across drug classes and sites of action.

Oxidative stress and reactive oxygen species (ROS)

Studies show that most ototoxic drugs increase reactive oxygen species (ROS) production in hair cells, spiral ganglion neurons, and stria vascularis cells. Excessive ROS production leads to lipid peroxidation, protein and DNA damage (especially mitochondrial DNA), and consequently to the activation of cell death pathways (Kamogashira et al., 2015; Tan and Vlajkovic, 2023).

Activation of apoptotic pathways

Oxidative stress and damage to nuclear and mitochondrial DNA initiate signaling cascades that lead to the apoptosis of hair cells and neurons. These include activation of stress kinases, increased expression of proapoptotic proteins (e.g., Bax), decreased levels of antiapoptotic proteins (e.g., Bcl-2), loss of mitochondrial membrane potential, release of cytochrome c, and activation of caspases (primarily 9 and 3). These mechanisms have been demonstrated in models of aminoglycoside and cisplatin ototoxicity (Kamogashira et al., 2015).

Disruption of ionic homeostasis

Ototoxic drugs may impair ionic conduction, especially that of potassium and calcium, leading to depolarization of hair cells, calcium overload, and secondary activation of Ca^2-dependent enzymes. Cisplatin can alter potassium conduction and decrease endolymphatic potential. This fact further increases hair cells' susceptibility to oxidative stress and apoptosis (Tan et al., 2023; Rose et al., 2024).

Vascular injury and stria vascularis

Loop diuretics, cisplatin, and other specific drugs cause edema and impair the stria vascularis. They interfere with endolymphatic potential and ion regulation. Reports also describe reduced blood circulation and injury to the blood-cochlear barrier as essential components that facilitate the retention of these drugs in the inner ear (Callejo et al., 2015; Steyger, 2021).

3.1.3. Mechanisms specific to aminoglycosides

Aminoglycosides exhibit high affinity for hair cells in the cochlea and dark cells in the vestibular labyrinth. Their toxic effect is a multi-step process.

Uptake via MET channels and other pathways

Research using mammalian models has shown that aminoglycosides primarily enter hair cells via mechanotransduction (MET) channels located at the tips of stereocilia. This block of channels markedly lowers cellular drug influx and, therefore, injury. It provides evidence for the key role of this entry mechanism (Alharazneh et al., 2011).

Inside the cell, aminoglycosides interact with membrane phospholipids and mitochondrial ribosomes. It inhibits protein synthesis and mitochondrial function. This process causes increased ROS production, a decline in mitochondrial membrane potential, and the triggering of apoptotic cascades. The injury usually starts in the outer hair cells of the basal turn of the cochlea, as indicated clinically by an early loss of high-frequency hearing (Rivetti et al., 2023; Steyger, 2021).

The role of oxidative stress and iron ion complexes

Iron ions catalyze Fenton reactions, and aminoglycosides bind to the iron. In animal models, they have been found to counteract the ototoxicity of aminoglycosides, thereby linking oxidative stress to this process.

3.1.4. Mechanisms specific to cisplatin

Cisplatin accumulates in the inner ear, particularly in the stria vascularis, hair cells, and spiral ganglion neurons. It is retained within cochlear tissues for months after the end of therapy, which explains the progressive and often irreversible nature of hearing loss (Callejo et al., 2015).

Oxidative stress and mitochondrial dysfunction

As antioxidants remove ROS, we can only say that cisplatin induces oxidative stress, damaging membranes, proteins, and DNA, or inhibiting the respiratory chain due to increased ROS generation in cochlear cells. This process leads to the disruption of matrix metalloproteinases (MMP), the release of cytochrome c, and the activation of the intrinsic apoptosis pathway (Callejo et al., 2015).

DNA damage and p53 activation

Cisplatin works by inhibiting DNA synthesis. It does this in both the cell nucleus and mitochondria by forming adducts. This, in turn, stimulates p53, upregulates Bax, and downregulates Bcl-2. Preclinical modulation of p53 signaling may reduce ototoxicity (Benkafadar et al., 2017).

Inflammatory processes and other forms of programmed cell death

In addition to classical apoptosis, evidence demonstrates the involvement of inflammatory reactions - characterized by NF-κB activation and the secretion of proinflammatory cytokines such as TNF-α and IL-1β, as well as other forms of programmed cell death, including ferroptosis and necroptosis. These phenomena, together with oxidative stress and DNA damage, increase the degeneration of hair cells and neurons (Steyger, 2021).

Stria vascularis dysfunction and ion transport disruption

Damage to the stria vascularis cells by cisplatin leads to a decrease in endocochlear potential, edema, and disruption of potassium transport. Consequently, the function of hair cells and spiral ganglion neurons is impaired, accelerating their degeneration (Callejo et al., 2015).

3.1.5. Other ototoxic drugs - mechanism overview

Loop diuretics (e.g., furosemide) act mainly on the stria vascularis by blocking the Na^+-K^+-$2Cl^-$ cotransporter. This process causes a decrease in cochlear potential and temporary impairment of hair cell function. However, studies show that at high doses or in combination with other ototoxic drugs, they can contribute to permanent hearing damage (Steyger, 2021).

Salicylates and NSAIDs are associated with modulation of the electromotility of outer hair cells. This process causes changes in ion conduction and disturbances in central auditory processing. They can cause reversible, mild hearing loss and tinnitus (Steyger, 2021).

Antimalarials (quinine, chloroquine) can have adverse effects on the microcirculation of the inner ear, hair cell metabolism, and neural conduction. Although most of the reported damage is reversible, cases of permanent hearing loss after long-term exposure have already been reported (Józefowicz-Korczyńska et al., 2021).

Modern targeted therapies and immunotherapies (tyrosine kinase inhibitors and immune checkpoint inhibitors) are increasingly associated with ototoxicity. However, the mechanisms underlying this phenomenon remain unclear to researchers. Studies suspect microvascular disorders and inflammation (Bonilla et al., 2025).

3.1.6. Interaction of ototoxic drugs with noise

A key element of the pathophysiology is the synergistic effect between ototoxic drugs and noise. Experimental studies in animals have demonstrated that moderate noise exposure, which does not cause permanent hearing loss on its own, can markedly increase the ototoxicity of aminoglycosides and cisplatin. Concurrent exposure to the drug and noise results in greater threshold shifts and more extensive hair cell damage than either factor alone (Steyger, 2021).

Probable mechanisms include increased opening of MET channels during noise exposure, which facilitates the uptake of cationic drugs (especially aminoglycosides) into hair cells. Another potential mechanism involves the accumulation of oxidative stress and the induction of inflammatory responses by both noise and drugs (Alharazneh et al., 2011; Steyger 2021). Table 1 presents the main groups of ototoxic medications, their mechanisms of action, and associated risk factors.

Table 1. Leading groups of ototoxic drugs - mechanism of damage, clinical symptoms

Drug group/examples	Main mechanism of inner ear damage	Type of hearing loss/symptoms
Aminoglycoside antibiotics (gentamicin, amikacin, tobramycin, kanamycin, streptomycin).	Entry into hair cells via MET channels; accumulation in outer hair cells and their mitochondria; increased production of reactive oxygen species (ROS); formation of complexes with iron ions (Fenton reactions); activation of apoptotic pathways; secondary damage to spiral ganglion neurons.	Bilateral, usually symmetrical, high-frequency sensorineural hearing loss; tinnitus is common; vestibular symptoms (vertigo, imbalance) may occur depending on the specific aminoglycoside
Platinum compounds (mainly cisplatin; less often carboplatin).	Accumulation of cisplatin in the cochlea (stria vascularis, hair cells, spiral ganglion neurons); increased oxidative stress and mitochondrial DNA damage; formation of DNA adducts and activation of p53; inflammatory response; dysfunction of the stria vascularis and reduction of endocochlear potential.	Bilateral, usually symmetrical, high-frequency sensorineural hearing loss; tinnitus is common; in children, impaired speech and language development and learning difficulties.
Loop diuretics (furosemide, bumetanide, torasemide, ethacrynic acid).	Blockade of the Na^+-K^+-$2Cl^-$ (NKCC1) cotransporter in the stria vascularis; disturbance of endolymph ionic composition; reduction of endocochlear potential; oedema and dysfunction of the stria vascularis.	Sudden, bilateral sensorineural hearing loss (often across a wide frequency range); tinnitus; sometimes aural fullness.
Salicylates and NSAIDs (high-dose acetylsalicylic acid, ibuprofen, naproxen, others).	Inhibition of outer hair cell electromotility; changes in cochlear ion conductance; modulation of central auditory pathway activity.	Bilateral, mild to moderate sensorineural hearing loss; tinnitus (often the first symptom); sometimes hyperacusis.
Antimalarial drugs (quinine, chloroquine, hydroxychloroquine).	Disturbances of inner ear microcirculation; possible direct toxicity to hair cells in the organ of Corti; impaired conduction in the vestibulocochlear nerve.	Tinnitus, vertigo; bilateral, usually mild to moderate sensorineural hearing loss.
Non-aminoglycoside antibiotics (macrolides - erythromycin, azithromycin, clarithromycin;	Mechanisms not fully understood; probably dysfunction of hair cells and cochlear microcirculation; for capreomycin -	Macrolides: usually reversible hearing loss and/or tinnitus (more frequent with i.v. administration

vancomycin; capreomycin).	ototoxicity similar to aminoglycosides; vancomycin often enhances the ototoxicity of other drugs rather than causing isolated damage.	and in renal failure); vancomycin: low risk of isolated ototoxicity, higher in combination with aminoglycosides; capreomycin: bilateral, often permanent sensorineural hearing loss.
Targeted therapies and immunotherapy (selected tyrosine kinase inhibitors, immune checkpoint inhibitors - PD-1/PD-L1, CTLA-4).	Disturbance of cochlear microcirculation; immune-mediated mechanisms (autoimmune labyrinthitis or neuritis of the eighth cranial nerve); possible direct neurotoxicity; frequent overlap with radiation-induced damage and other toxic insults.	Heterogeneous clinical picture: sudden unilateral or bilateral sensorineural hearing loss, often with tinnitus; vestibular symptoms may accompany hearing loss; in some cases, presentation similar to autoimmune inner ear disease.
Other "emerging ototoxic drugs" (some proton pump inhibitors, immunosuppressants, biological agents, selected cardiologic and oncologic drugs).	Mechanisms poorly understood; most data come from pharmacovigilance databases and case reports; possible role of microcirculatory disturbances, oxidative stress or immune-mediated mechanisms.	Usually, single cases of sensorineural hearing loss (often unilateral) and/or tinnitus; vestibular symptoms may sometimes accompany hearing loss.

3.2. Ototoxic drugs - clinical characteristics

In the clinical setting, the most important groups of ototoxic medications are: aminoglycoside antibiotics; platinum-based compounds; loop diuretics; salicylic acid and other nonsteroidal anti-inflammatory drugs; antimalarials; with an increasing number listed in types such as selected non-aminoglycoside antibiotics, targeted drugs, and immunotherapy. A young feature is injury to hair cells, spiral ganglion neurons, and the stria vascularis, often in an accumulative dose-dependent fashion and with the impact of concurrent risk factors.

3.2.1. Aminoglycoside antibiotics

A key symptom of this side effect is bilateral sensorineural hearing loss, which usually begins at high frequencies. Known risk factors from documented reports to date include high total dose, high Cmax, and/or escalating trough levels or minimum concentrations, prolonged treatment duration, young advanced age in the neonatal period, pre-existing hearing loss before drug, renal etiology, concurrent nephrotoxic agents (e.g., cisplatin, loop diuretics, vancomycin) as aetiological or etiological cause of distinct hearing impairment (Selimoglu, 2007; Dillard et al., 2021).

MT-RNR1 screening is currently being considered for specific high-risk populations, including patients with cystic fibrosis.

Epidemiological data - drug-resistant tuberculosis. A meta-analysis of 18 studies from 10 countries estimated that approximately 40% of patients with drug-resistant tuberculosis (DR-TB) treated with aminoglycosides develop ototoxic hearing loss (Dillard et al., 2021). The authors emphasize that, globally, this accounts for thousands of preventable cases of permanent hearing loss annually, a finding that supports the WHO's shift away from injectable aminoglycosides in DR-TB treatment regimens.

Epidemiological data - cystic fibrosis. In patients with cystic fibrosis, repeated intravenous administration of aminoglycosides (especially tobramycin) leads to a significant increase in the risk of high-frequency hearing loss. Classic studies have already demonstrated the presence of bilateral high-frequency hearing loss in up to 15-20% of adult patients. More recent studies have shown that a single course of intravenous tobramycin (11-22 days) can cause measurable ototoxicity in the vast majority of patients when sensitive ASHA criteria are used, and reviews emphasize the high risk of ototoxicity in people with CF due to the accumulation of multiple courses of aminoglycosides over their lifetime.

3.2.2. Platinum Compounds

Cisplatin is the most widely used therapeutic agent for pediatric as well as adult cancer treatment. Its ototoxicity mainly affects the cochlea. Clinical symptoms include symmetrical sensorineural hearing loss, with younger patients being particularly vulnerable. It involves high frequencies. Patients may experience tinnitus (Romano et al., 2020).

The rate of platinum ototoxicity in children is estimated to be 40 to 60%. In some high-risk groups, this number can reach 60-90%. In the randomized SIOPEL-6 study, which included children with hepatoblastoma, researchers found that 63% of patients treated with cisplatin alone experienced hearing loss (Brock ≥1). Delayed administration of sodium thiosulfate reduced this percentage to 33% (Brock et al., 2018).

Studies have also highlighted a strong link between platinum-induced hearing loss and delayed speech in young patients. These difficulties can affect learning outcomes and overall quality of life. The most common risk factors for ototoxicity caused by cisplatin use are high cumulative doses. Other risk factors include the cycle intervals and the simultaneous use of other ototoxic agents. Previous hearing loss, cranial radiotherapy, and genetic factors are also significant.

3.2.3. Loop diuretics

Examples: furosemide, bumetanide, torasemide, ethacrynic acid.

Loop diuretics are toxic to the stria vascularis, where they block Na^+-K^+-$2Cl^-$ co-transport (also referred to as NKCC1). The latter process, in turn, leads to a rapid reduction in the endocochlear potential and disruption of ionic homeostasis within the endolymph. This process causes temporary dysfunction of hair cells and conduction in the auditory pathway and system (Ding et al., 2016).

Clinically, this usually manifests as sudden bilateral sensorineural hearing loss. The effect is often reversible if the patient discontinues treatment. The risk of permanent hearing loss increases significantly with very high doses and rapid intravenous administration. Concurrent renal impairment and the use of other ototoxic agents (e.g., aminoglycosides, cisplatin) will further elevate the risk (Ding et al., 2016).

Doctors should be cautious when administering high doses of furosemide in newborns, premature infants, patients with moderate to severe renal failure (renal blood flow and tubular secretion of furosemide will decrease), and elderly patients (normal aging may alter drug disposition).

3.2.4. Salicylates and NSAIDs

A classic example of salicylate ototoxicity is the administration of acetylsalicylic acid at high doses (several grams per day). Symptoms include tinnitus and reversible, usually bilateral sensorineural hearing loss, which can reach up to 30-40 dB in the mid- to high frequencies. The symptoms typically disappear within a few days following discontinuation of the drug. Studies indicate that the primary site of action is the outer hair cells; inhibition of their electromotility is evidenced by reduced otoacoustic emissions.

Regarding other NSAIDs (ibuprofen, naproxen, diclofenac, etc.), ototoxicity is usually milder and also reversible. However, epidemiological studies have shown that regular, long-term use of high doses of analgesics (aspirin, NSAIDs, paracetamol) is associated with a significantly increased risk of permanent hearing loss (Curhan et al., 2010). In clinical practice, it is essential to be aware of combinations of potentially ototoxic drugs. Patients should be informed of the possibility of temporary tinnitus or hearing loss when using high doses.

3.2.5. Antimalarial drugs (quinine, chloroquine, hydroxychloroquine)

Antimalarial drugs are among the classic ototoxic drugs known in medicine. Studies show that these drugs can cause tinnitus and dizziness. Sensorineural hearing loss caused by these drugs is usually temporary. However, there have been reports of irreversible changes in hearing threshold after prolonged exposure or high doses (Józefowicz-Korczyńska et al., 2021).

Studies have shown that chloroquine can be cytotoxic to the hair cells of the organ of Corti. This process leads to dose-dependent cell death. The cases described in humans indicate microvascular dysfunction of the inner ear and an increased risk of adverse effects when used concomitantly with other ototoxic agents. We must note that there may be overestimations in patients using hydroxychloroquine for the prevention or treatment of COVID-19 (Józefowicz-Korczyńska et al., 2021; Reynard and Thai-Van, 2024).

3.2.6. Other ototoxic drugs

A detailed examination by Józefowicz-Korczyńska et al., (2021) focused on the ototoxicity of non-aminoglycoside antibiotics (non-AMG antibiotics), including capremycin, macrolides (erythromycin, azithromycin, and clarithromycin), and vancomycin. Macrolidescan can induce reversible hearing loss and tinnitus, particularly in newborns, in patients with renal insufficiency, and with high intravenous doses. Vancomycin has classically been considered an agent with the potential for ototoxicity. The combination of vancomycin and aminoglycosides, however, substantially increases the risk.

Targeted drugs and immunotherapy. Recent studies have shown a link between tyrosine kinase inhibitors and other targeted drugs (e.g., selective EGFR, BRAF, or MET inhibitors) and ototoxicity. These reports concern individual cases or collections of adverse events reported after the drugs were marketed (Reynard and Thai-Van, 2024). Researchers are increasingly investigating possible hearing damage during immunotherapy - a review of cases of ototoxicity during treatment with checkpoint inhibitors (PD-1/PD-L1, CTLA-4) suggests that the mechanism may be immunological in nature (inflammation of the VIII nerve, inflammation of the cochlea). Some patients have shown improvement after intensive immunosuppressive treatment (Wierzbicka et al., 2024).

3.3. Otoprotective strategies

3.3.1. Non-pharmacological strategies

The non-pharmacological approach to hearing protection primarily involves adjusting the medication dose. Physicians should also control risk factors (kidney function, other ototoxic drugs) and advise patients to limit their noise exposure. Review articles and guidelines on ototoxicity recognize these measures as the first-line treatment for all patients receiving ototoxic drugs. We should pursue these measures regardless of pharmacological hearing protection measures (Lindeborg et al., 2022; Romano et al., 2020; Lee et al., 2024).

3.3.2. Modification of dosage and administration schedules

In the case of cisplatin, the most critical risk factor may be the cumulative dose. The current trend is to provide daily, but cyclical, administration of a smaller dose rather than a single, high dose (Romano et al., 2020; Lee et al., 2024).

Studies suggest that daily administration of aminoglycosides, rather than multiple-dose regimens, has lower ototoxic potential while maintaining antibacterial activity. Some updates even mention lower ototoxic potential (Rivetti et al., 2023; Lindeborg et al., 2022).

However, the same is accurate for therapeutic drug monitoring of peak (especially in the case of gentamicin and amikacin) and trough concentrations - do not elevate the top concentration or leave the bottom concentration too high, so that accumulation occurs only inside hair cells (Rivetti et al., 2023).

3.3.3. Treatment and kidney function

Patients with kidney problems are more susceptible to the toxic effects of ototoxic drugs. To prevent this, oncologists follow guidelines that require intensive hydration and the use of diuretics on treatment days (Lindeborg et al., 2022; Romano et al., 2020; Lee et al., 2024). Three aminoglycosides and two nephrotoxic and ototoxic drugs caused dose-dependent acute renal dysfunction (Rivetti et al., 2023). It is essential to limit the use of multiple ototoxic drugs (Lindeborg et al., 2022; Rivetti et al., 2023; Reynard & Thai-Van, 2024).

3.3.4. Limiting exposure to noise and audiological monitoring

There is ample evidence of a combined effect between noise exposure and the drug's harmful effects. Current recommendations state that patients taking these drugs should avoid loud noise during and after treatment. This procedure includes concerts, clubs, and running industrial machinery. Doctors should encourage patients to use hearing protection (e.g., earmuffs or earplugs) (Lindeborg et al., 2022; Lee et al., 2024). Hearing tests should be performed before, during, and after treatment (Romano et al., 2020; Lindeborg et al., 2022; Lee et al., 2024).

3.3.5. Pharmacological strategies - an overview of otoprotectants

Pharmacological otoprotection is an emerging field that, however, has so far resulted in sodium thiosulfate (STS) registration based solely on the successful prevention of cisplatin ototoxicity in children with specific solid tumors through well-conducted randomized phase III studies (Freyer et al., 2017; Brock et al., 2018; Meijer et al., 2024). All other compounds-antioxidants, uptake blockers, and

signaling pathway modulators-still remain mainly in the preclinical or early clinical phase of development and are regarded as potentially promising (experimental) (Lee et al., 2024).

3.3.6. Thiol compounds and antioxidants

Sodium thiosulfate is a small-molecule thiol compound that can combine with reactive platinum metabolites as well as free radicals of oxygen in the cochlea (Freyer et al., 2017; Meijer et al., 2024). Administration of intravenous sodium thiosulfate (STS) at 20 g/m², starting six hours after cisplatin (80 mg/m²), reduced the rate of clinically relevant ototoxicity from 63% to 33% in children with standard-risk hepatoblastoma treated within the randomized SIOPEL-6 trial, without a significant compromise in overall and event-free survival (Brock et al., 2018).

In the multicenter ACCL0431 study involving children with various cancers, researchers administered STS with a delay (16 g/m² administered 6 hours after cisplatin). The study showed that this intervention reduced the risk of ototoxicity by approximately 50%. This study also considered the potential negative impact on a small group of patients with metastatic disease (Freyer et al., 2017; Meijer et al., 2024).

According to the latest studies and guidelines, STS has been recognized as the first registered otoprotective drug for children and young adolescents with localized solid tumors undergoing cisplatin therapy (Meijer et al., 2024; Lee et al., 2024).

N-acetylcysteine (NAC)

NAC is a precursor to glutathione and a powerful antioxidant. Numerous animal studies have shown that it shields the auditory organ from cisplatin and aminoglycoside exposure. This evidence has also been confirmed in human studies (Hammill and Campbell, 2018; Lee et al., 2024). In a phase I study, researchers administered intravenous cisplatin to children with solid tumors, followed immediately by NAC. The patients tolerated the intervention well, and this approach likely reduced the incidence of ototoxicity. However, it is unclear how strong the evidence is (Orgel et al., 2023).

Transtympanic administration of NAC has been the subject of a small pilot study; however, the data remain inconclusive (Hammill and Campbell, 2018; Lee et al., 2024). D-methionine is an amino acid. It has antioxidant and antiapoptotic effects. In many animal models, it protects against the effects of ototoxic drugs. To date, researchers have not yet conducted any extensive randomized studies (Hammill and Campbell, 2018; Lee et al., 2024).

Amifostine, a non-specific thiol cytoprotectant, has been suggested in individual studies to offer some protection against cisplatin ototoxicity. The latest research indicates that there is still no firm evidence of their effectiveness. In addition, they appear to cause several side effects. Therefore, clinicians should not use these agents solely for hearing protection (Freyer et al., 2017; Hammill and Campbell, 2018; Meijer et al., 2024). Similar conclusions apply to tocopherol and to other antioxidants such as alpha-lipoic acid, glutathione, vitamins C and E, resveratrol, and coenzyme Q10 (Hammill and Campbell, 2018; Lee et al., 2024).

3.3.7. Drugs acting on channels and transporters

The pharmacological blockade of ototoxic drugs entering hair cells is very interesting. Aminoglycosides, like Cisplatin, enter cells through MET channels and/or specific membrane transporters. Blocking these pathways could limit drug penetration into these structures (Kros & Steyger, 2019; Lee et al., 2024). The main compound mentioned in the studies is ORC-13661. It reduces ototoxicity by reversibly blocking MET channels. This action keeps the drug from entering hair cells. Animal studies show it can protect hair cells from aminoglycosides and cisplatin. This process likely leads to dose-dependent hearing protection (Kros & Steyger, 2019; Lee et al., 2024).

3.3.8. Other pharmacological approaches

Preclinical models have shown that caspase inhibitors, JNK pathway modulators, anti-inflammatory drugs, and ferroptosis inhibitors have protective effects (Orgel et al., 2023). While some of these molecules are only entering early-phase clinical trials, animal models currently provide most of the data. Consequently, at this stage, no drug from this group is routinely recommended for the prevention of ototoxicity in humans (Lee et al., 2024).

3.3.9. Route of administration of otoprotectants

The mode of delivery for an agent is a key factor in any otoprotectant approach. The route of administration makes no difference in the drug's effect. However, systemic application avoids any uneven distribution throughout the liver that can occur after trans-arterial delivery (as with STS in ACCL0431 and SIOPEL-6), but it also has the downside of interfering with anticancer actions (Freyer et al., 2017; Brock et al., 2018; Meijer et al., 2024). Therefore, STS is administered after a delay to reduce the effect on tumor platinum exposure (Freyer et al., 2017; Meijer et al., 2024).

Methods such as administering drugs through the eardrum are still in the research phase (Lee et al., 2024; Meijer et al., 2024). Other methods under investigation include nanoparticle carriers and implantable devices, but all are still in the preclinical or early clinical phases (Lee et al., 2024). Recent reviews have shown that no other hearing protection measures can be recommended for children with tumors other than localized tumors (for which intravenous STS is used) (Romano et al., 2020; Freyer et al., 2017; Lee et al., 2024). Table 2 shows the principal risk factors and possible hearing protection strategies.

Table 2. Risk factors for ototoxicity and recommended otoprotective measures

Risk factor	Most commonly involved (examples)	Recommended otoprotective measures
Extreme age (infants, children <5 years, elderly patients)	Cisplatin, carboplatin, aminoglycosides	Careful dose selection; consideration of less ototoxic regimens whenever possible; more frequent hearing monitoring (including high-frequency audiometry and otoacoustic emissions).
Pre-existing hearing loss / inner ear damage	All ototoxic drugs	Avoidance of highly ototoxic drugs; consideration of alternative therapies; intensive hearing monitoring; early fitting of hearing aids if further deterioration occurs.
Impaired renal function - reduced glomerular filtration rate (GFR), renal failure)	Cisplatin, aminoglycosides, other nephro- and ototoxic drugs	Dose adjustment according to GFR; extension of dosing intervals; strict therapeutic drug monitoring (TDM) for aminoglycosides; consideration of switching to less nephro-/ototoxic agents.
Mitochondrial MT-RNR1 mutations (e.g. m.1555A>G)	Aminoglycosides (gentamicin, amikacin, tobramycin)	Avoidance of aminoglycosides in carriers where possible; consideration of pharmacogenomic testing in high-risk populations; use of alternative antibiotics.
High cumulative cisplatin dose (>300-400 mg/m²)	Cisplatin (especially in children and young adults)	Limiting cumulative dose when oncologically feasible; dose fractionation; consideration of switching to carboplatin in selected indications; use of otoprotective agents (e.g. sodium thiosulfate).
Long treatment duration, high peak concentrations and elevated trough levels	Aminoglycosides (especially i.v. in repeated courses)	Once-daily dosing regimens; therapeutic drug monitoring; keeping treatment duration as short as possible; avoidance of unnecessary repeated courses.
Concomitant use of multiple ototoxic drugs	Cisplatin + aminoglycosides; loop diuretics; vancomycin	Avoid combinations whenever possible; if unavoidable - dose reduction, strict

		TDM, intensive monitoring of hearing and renal function; documentation of the total ototoxic burden.
Noise exposure (occupational noise, concerts, clubs, loud headphones)	Cisplatin, aminoglycosides, other ototoxic drugs	Patient education; avoidance of loud environments during treatment and for several months after its completion; use of hearing protection (earplugs, earmuffs).

3.4. Directions for future research and challenges

The most recent randomized studies on hearing protection with STS in children treated with cisplatin include those by Brock et al., (2018), Freyer et al., (2017), and Meijer et al., (2024). More clinical studies involving adult patients are needed, especially if they are taking other ototoxic drugs. The discovery of a particular genetic predisposition opens the door to otoprotection in patients with mutations, especially m.1555A>G (Rivetti et al., 2023; Guan, 2011). It is, however, necessary to more accurately identify populations and clinical settings in which genetic FDR (Genetic False Discovery Rate) has a real influence on therapeutic decision-making, and to determine how best to incorporate this into standard care pathways.

Research on regrowth: Therapy for increasing specialty care. The field of interventions to regenerate cell therapies and small molecules. Reviews note that, despite regeneration of auditory cells in lower animals, this is not achievable in human cells. An additional challenge is the implementation and application of the methods discovered. Although guidelines for monitoring ototoxicity exist, they are implemented unevenly (Konrad-Martin et al., 2018). Future research must investigate new compounds, organizational models, costs, effects, and pragmatic implementation in resource-poor settings.

4. CONCLUSION

Ototoxicity is still a common and underappreciated drug-induced adverse effect resulting in permanent hearing loss and/or balance disorder in a high number of patients, especially when being treated with platinum-containing cytostatics or aminoglycosides. In adults, this leads to a worse quality of life and brain function, whereas in children, the consequences are defective development of speech, learning problems at school, and truncated potential psychosocial and professional existence. Based on the current state of knowledge, one can conclude that non-drug approaches are likely to be more realistic otoprotective options or noise reduction/hearing surveillance regularly – especially in children and for all risk groups under long-term treatment.

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Data and materials availability

All data associated with this study are present in the paper.

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