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Chapter 13

Ototoxicity: Old and New Foes

Agnieszka J. Szczepek

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Abstract

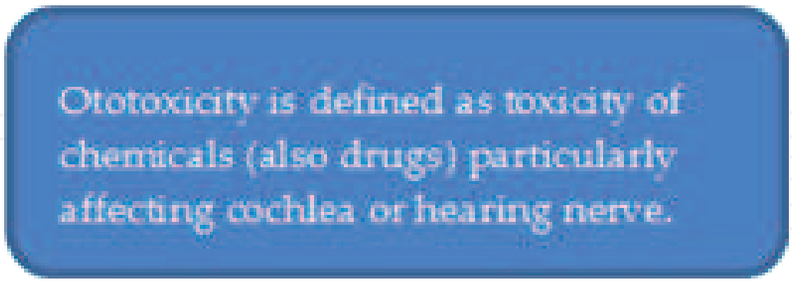
Drug-induced ototoxicity has been known for centuries. Already in the seventeenth century, hearing loss was described to be a side effect of quinine. The post- World War II pharmaceutical industry boomed with the production of aminoglycoside antibiotics followed by diuretics and cytostatic drugs. Wide-spread and long-term usage of these medications brought the knowledge about their unwanted ototoxic effects. In the last decades, several new drugs appeared on the shelves of pharmacies and the hearing loss or tinnitus have been among the side effects of many of them. However, the awareness of community about new ototoxic medications is still not sufficient. New ototoxic drugs may belong to the class of phosphodiesterase-5 (PDE5) inhibitors, used to improve microcirculation and to treat erectile dysfunction. Moreover, interferons used for the therapy of hepatitis B and C, common painkiller paracetamol and hydrocodone, synthetic opioid methadone and the inhibitors of reverse transcriptase were demonstrated to induce adverse effects on hearing. Lastly, hearing loss linked to immunosuppressive drugs was documented in patients undergoing organ transplantation. Making the patients aware of adverse drug reactions and offering them audiological monitoring and intervention should be considered by respective therapists.

Keywords: ototoxic drugs, viral infections, reverse transcriptase inhibitors, interferons, PDE5 inhibitors, immunosuppressants, hearing loss, adverse reactions

1. Introduction

The sense of hearing is fundamental to the communication and proper reaction to dangerous situations. Moreover, recent studies indicated that the hearing loss increases significantly the risk of dementia [1]. Unfortunately, people's ability to hear deteriorates with time, as the human auditory epithelium is post-mitotic and unable to regenerate. In other

words, the few thousand of auditory hair cells with which we are born have to last our entire life. There are several causes of hearing loss such as noise, aging, infections, tumors, neuronal degeneration or cardiovascular diseases. Another important cause of hearing loss is ototoxicity.



In this chapter, we will concentrate on medications that are known to induce hearing loss as an adverse effect. These medications are also known as ototoxic medications.

Clinical signs of ototoxicity may include at least one of the following symptoms:

- tinnitus
- hearing loss (unilateral or bilateral)
- vertigo.

First signs of ototoxicity usually develop during or shortly after receiving particular medication. Majority of ototoxic drugs induces irreparable damage translating into permanent hearing loss; however, **aspirin and derivatives** belong to drugs that cause most of the times **reversible hearing loss** [2]. In fact, aspirin-induced ototoxicity in form of tinnitus was used for decades by rheumatologists to adjust the maximal therapeutic dose of salicylates in the patients. This practice was abandoned because of poor correlation between salicylate blood levels and ototoxicity symptoms [3] and because of development of new drugs used for the treatment of rheumatic diseases. Nevertheless, even today there are patients occasionally admitted to the emergency room because of the salicylate-induced ototoxicity [4]. The ototoxicity of salicylate has been attributed to its capacity to bind and inhibit the action of cochlear protein **prestin**, expressed by the outer hair cells [5, 6]. In addition, salicylate can induce **death of spiral ganglion neurons** as well as cause **dysregulation in the central auditory pathway** [7].

Other groups of well-known ototoxic drugs that frequently cause **hearing loss** include:

- platinum-based cytostatic drugs
- aminoglycoside antibiotics
- loop diuretics

Platinum-based cytostatics (**cisplatin**, **carboplatin** and **oxaliplatin**) are used as single agents and in combination with other drugs for the treatment of various types of cancer (e.g., testicular carcinoma, lung carcinoma, ovarian carcinoma, head and neck carcinomas, melanomas,

lymphomas and neuroblastomas) [8]. The platinum-based drugs bind DNA and induce irreversible changes that prohibit tumor cell division. However, common adverse effects of platinum-based drugs include nephrotoxicity and ototoxicity. This toxicity is being attributed to an excessive production of reactive oxygen species that leads to death of auditory hair cells [9–11]. Clinically, patients develop **permanent bilateral hearing loss that originates in high frequencies** [12]. In addition, patients may have **difficulties with speech understanding in noise** [13].

Aminoglycosides are a group of antibiotics used to treat gram-negative bacterial and mycobacterial infections. Clinically used aminoglycosides include amikacin and kanamycin (primarily cochleotoxic) as well as gentamicin, streptomycin and tobramycin (primarily vestibulotoxic) [14]. Similar to the ototoxic mechanism of platinum-based drugs, aminoglycosides induce excessive formation of free oxygen species followed by apoptosis of sensory hair cells [10, 15]. The aminoglycoside-induced hearing loss **is bilateral and permanent and starts in the high frequencies**. Precisely because of its ototoxic properties, gentamicin is frequently used for the treatment of Ménière's disease in the form of intratympanic injections to deplete the vestibular hair cells and thus, to prevent frequent vertigo attacks.

Of note: About 30% of the world population is infected with *Mycobacterium tuberculosis* [16]. The treatment of tuberculosis (especially that caused by **multiple-drug resistant *Mycobacterium tuberculosis***) includes intravenous administration of so-called ond-line antibiotics–amikacin, kanamycin and streptomycin–leaving at least 20% of the patients with serious permanent hearing impairment [17].

Loop diuretics are a group of drugs that inhibit renal reabsorption of sodium, chloride and potassium. They are often used to treat kidney insufficiency or heart failure. Loop diuretics include furosemide, bumetanide, ethacrynic acid and torsemide. Their ototoxic mechanism involves inhibition of potassium resorption occurring in the stria vascularis and consequent **decrease in the endocochlear potential** [18]. The hearing loss induced by loop diuretics is **bilateral and usually reversible;** however, since loop diuretics are known to synergize with platinum-based drugs or with aminoglycosides in their ototoxic action, in patients receiving drugs from both groups, loop diuretics may worsen the degree of permanent hearing loss [19–21].

There is a growing number of case reports and larger studies indicating that the family of ototoxic drugs is growing and embraces newly developed medications. Although the ototoxic properties of several pharmacological drugs were recently compiled in an excellent review written by Cianfrone et al. [22], the clinical information changes and requires update.

In this chapter, we review selected group of frequently used, contemporary pharmacological drugs (phosphodiesterase-5 blockers and antiviral drugs (see **Table 1**), painkillers and immunosuppressants) in aspect of audiologically important adverse reactions including hearing loss and tinnitus.

The class of medication	Type of report	Presence of tinnitus	Type of hearing loss	Measuring method	Reversibility of hearing loss	References
PDE5 inhibitors	Case report (1 subject)	Not stated	Profound bilateral sensorineural hearing loss	Pure tone audiometry; impedance audiometry; stapedial reflex absent on both sides	No	[23]
	Prospective study (21 subjects)	Not stated	Unilateral sensorineural hearing loss 1 h after injection of drug	Pure tone audiometry	Yes	[24]
	Analysis of 47 case reports (pharmacovigilance)	Not stated	Unilateral or bilateral sensorineural hearing loss	Not stated	In some cases, yes; in others long-term impairment	[26]
	Case report (2 subjects)	Yes	Unilateral sensorineural hearing loss	Pure tone audiometry, ABR	In one case, yes	[27]
Interferons	Prospective study (before/after) 49 subjects	Yes	Sensorineural hearing loss	Pure tone audiometry, tympanometry (normal)	Yes	[30]
	Case report (3 subjects)	Yes	Unilateral sensorineural hearing loss	Pure tone audiometry	Yes (2 cases), no (1 case)	[31]
	Prospective study (before/after) 73 subjects	Yes	Sensorineural hearing loss	Pure tone audiometry	Yes	[31]
PEG interferons	Prospective study (before/after) 21 subjects	Not stated	None found	Pure tone audiometry, DPOAE	Not applicable	[35]
	Case report (1 subject)	Not stated	Unilateral hearing loss	Not stated	Yes	[36]
	Case report (1 subject)	Yes	Unilateral hearing loss	Not stated	No	[37]
	Case report (6 subjects)	Yes (4 of 6)	Five subjects developed unilateral and one bilateral sensorineural hearing loss	Pure tone audiometry	No improvement in three cases, some improvement in two cases, no data in one case	[38]

Although in the industrialized countries, the hepatitis C and B therapy with pegylated or non-pegylated interferons and ribavirin is being replaced by other pharmacological regimes, one should not ignore the fact that not all countries and hospitals have adopted the new routine and that the interferons are still in use, possibly contributing to drug-related hearing loss.

Table 1. Summary of clinical reports describing hearing loss in PDE5- and interferon-treated patients.

2. Phosphodiesterase-5 (PDE5) inhibitors

PDE5 inhibitors block the phosphodiesterase-5 in the smooth muscle cells lining the blood vessels in the cardiovascular system. Phosphodiesterase-5 degrades cyclic GMP, regulating smooth muscle tone. The first PDE5 inhibitor–sildenafil–was introduced in the market in 1998 under the name Viagra. PDE5 inhibitors are used for the treatment of erectile dysfunctions and for pulmonary artery hypertension.

In the year 2007, an alarming report was published by Mukherjee and Shivakumar, in which a case of bilateral profound sensorineural hearing loss was described in 44-year-old man who took 50 mg/day of sildenafil for 2 weeks [23]. Based on that report, **FDA issued a warning about possible sudden hearing loss among users of PDE5 inhibitors**.

Over the past 10 years, evidence suggesting negative influence of PDE5 inhibitors on hearing has accumulated. In a clinical study, Okuyucu et al. [24] reported significant but reversible unilateral hearing loss in four of 18 patients taking PDE5 inhibitors. The hearing loss affected the right ear at 10,000 Hz ($p = 0.008$).

Much larger epidemiological study published 1 year later by McGwin [25] evaluated the relationship between hearing loss and the use of PDE5 inhibitors in a population-based sample. This USA-based study was designed using self-reported hearing impairment and PDE5i use and included over eleven thousand men who were 40 years or older. Results of this study indicated that men with hearing loss are more than twice as likely to use PDE5 inhibitors, when compared with those not reporting hearing loss. However, no causal relationship could be established in that study.

In 2011, Khan et al. [26] published a report based on data provided by pharmacovigilance agencies Europe, the Americas, East Asia and Australasia, and on published reports. The authors identified among PDE5 inhibitor users 47 cases of sensorineural hearing loss, most of them unilateral. Almost 70% of the subjects (mean age 56.6 years, men-to-women ratio 7:1) reported hearing loss within 24 h after ingestion of PDE5 inhibitors.

In 2012, unilateral sudden sensorineural hearing loss affecting two male PDE5 inhibitor users (age 37 and 43) was described by Barreto and Bahmad [27]. Unfortunately, neither the time after the hearing loss has occurred nor the dosage of PDE5 inhibitors was stated. In addition to the hearing loss, both patients were affected by vertigo and tinnitus. After combination therapy consisting of steroids administered orally and intratympanically, one of the patients recovered partially, whereas the other one was left with permanent profound sensorineural hearing loss.

The causal relationship between the PDE5 inhibitors and (sudden) sensorineural hearing loss remains to be confirmed using experimental models. Au and colleagues using the animal model (C57BL/6J mice) and sildenafil (Viagra) were unable to find the differences in hearing thresholds between the drug- and placebo-treated animals [28]. However, other functional studies in mice with the use of osmotic pumps for drug release demonstrated that the inner ear of animals exposed to sildenafil reacted with hydrops [29].

The epidemiological and case report data indicate that PDE5 inhibitors may have general negative impact on hearing. Moreover, PDE5 inhibitors may induce sudden sensorineural hearing loss that in some cases can be successfully treated with corticosteroids; in some other cases, the patients recover without any treatment; and lastly, it can also leave patients with permanent hearing impairment.

3. Antiviral medications

3.1. Interferons

Interferons (IFN) are a group of naturally occurring proteins that are released by several cell types in response to infection or tumors. There are three classes of interferons: type I, type II and type III. Type I interferons include IFN-alpha and IFN-beta. Synthetic and recombinant interferons, alpha and beta, have been used for therapy of viral infections with hepatitis C or B virus. In addition, IFN-beta can be used to treat multiple sclerosis.

One of the first reports associating interferon treatment with hearing loss was published in 1994 [30]. In that report, a group of 49 patients (32 men and 17 women, mean age 48.6, age range 23–67) receiving various brands of interferons for chronic hepatitis B or C were assessed with pure tone audiometry before the onset of treatment and then in consecutive 1-week interval. In case of IFN-alpha, the drug was administered i.m. each day for 2 weeks and then three times a week for 14–22 weeks. In case of IFN-beta, the drug was administered i.v. daily for 6 weeks. The study demonstrated that 45% (22 patients) developed auditory dysfunction: 14 patients (29%) reported having tinnitus and 18 patients (35%) were diagnosed with sudden sensorineural hearing loss. More than half (56%) of the patients treated with interferon-beta (total of 27 subjects) developed auditory disability with unilateral or bilateral hearing loss affecting various frequencies diagnosed in 11 patients (41%). In the group treated with IFN-alpha (total of 22 subjects), seven developed unilateral hearing loss affecting 8000 Hz. Progressive hearing loss leads in two cases to withdrawal from therapy. There was no association between the clinical parameters such as proteinuria, leucopenia, liver functions and the hearing loss. Interestingly, all patients recovered within 2 weeks after finishing the interferon treatment.

Published 1 year later, prospective audiological study of 73 patients treated with IFN-alpha or IFN-beta for hepatitis confirmed the above observations, including the hearing loss exclusively affecting 8000 Hz in patients receiving IFN-alpha [31]. There was, however, one difference: in the larger sample studied, the hearing abilities of one patient have not recovered after discontinuation of therapy. Later, studies confirmed majority of these observations [32] and most importantly the general reversibility of ototoxic effects of IFN-alpha [33].

Interesting mechanistic insights of IFN-alpha-induced ototoxicity were delivered from studies using mouse model [34]. There was an elevated ABR threshold in mice treated with IFN-alpha as compared to untreated control group. Moreover, histological findings of cochleae dissected from experimental animals indicated abnormalities in the number (lower) and appearance (cytoplasmic vacuolization) of the spiral limbus fibroblasts in the IFN-alpha-treated mice.

These findings point to direct negative effect of IFN-alpha on cochlear biology, which may result in the hearing loss.

3.2. Pegylated interferons and ribavirin

Pegylated interferons are chemically "improved" interferons bound to polyethylene glycol (PEG). Pegylation assures longer half-time of interferons in the body. There are three groups of pegylated interferons available in the market–pegylated interferon-alpha-2a (PEG-IFNa2a), pegylated interferon-alpha-2b (PEG-IFNa2b) and pegylated interferon-beta-1a.

Ribavirin is a guanosine analog (nucleoside inhibitor) that stops viral RNA synthesis. It is used to treat various viral hemorrhagic fevers, and it is the only known drug against rabies. Although new therapeutic approaches are being introduced on the healthcare market for the treatment of hepatitis C (e.g., protease inhibitor telaprevir or boceprevir), ribavirin in combination with PEG-IFN-alpha is still a part of the current standard of care (SOC) therapy in some countries and it is also included in the new therapeutic regime.

Therapeutic use of PEG-IFN and ribavirin in hepatitis C infections induces similar otological effects as the therapy with non-pegylated interferons only. However, there is one major difference: the hearing abilities do not recover in the majority of cases. Although some reports describe no hearing disabilities [35] or sudden unilateral sensorineural hearing loss resolving spontaneously within 2 weeks after the end of treatment [36], some other demonstrate that patients may develop irreversible unilateral hearing loss [37] or irreversible unilateral pantonal hearing loss (measured by pure tone audiometry) and tinnitus [38].

3.3. Inhibitors of viral reverse transcriptase

According to the United Nations AIDS organization, approximately 36.7 million people worldwide are infected with the HIV virus. The patients with HIV are treated with drugs that inhibit the virus proliferation. Since HIV virus uses very unique enzyme to copy its genome, this enzyme–reverse transcriptase–is a pharmacological target of anti-HIV therapy. The unique thing about the HIV therapy is that it should never be stopped, even if the viral load is undetectable.

The discovery and the beginning of clinical application of reverse transcriptase inhibitors date back to the eighties last century. The first reports about their negative effect on hearing appeared some 10 years later and ever since conflicting conclusions are being drawn from several studies. In some studies, authors found the hearing loss among 30% of HIV patients taking the reverse transcription inhibitors [39–41], whereas in other studies, no association between audiological impairment and antiviral medication was found [42, 43]. Various inclusion criteria, diverse outcome measure methods, sample size and many other factors could contribute to these dissimilar results.

In the controlled environment of experimental laboratory, the results look much more uniform and point at universal ototoxicity of all types of reverse transcriptase inhibitors that are on the market, as measured by the viability of auditory epithelial cell line exposed to various concentrations of 14 types of pharmacological reverse transcription inhibitors as single agents and in combination, as used in the clinics [44].

4. Paracetamol (acetaminophen) and hydrocodone

Paracetamol, also known as acetaminophen (in the USA and Canada) or APAP, is the most commonly used pain killer in North America and Europe. It inhibits selectively cyclooxygenase-2 (COX-2) and may also exert other pain-relieving functions. Recent studies on self-reported professionally diagnosed hearing loss and use of analgesics indicated that regular use of paracetamol significantly increases the risk of hearing loss in men [45] and women [46]. The large size of samples with which the studies were performed (26,917 men and 62,261 women) makes both studies particularly credible.

The main conclusion from this study was that the long-term use of paracetamol (acetaminophen) increases the risk of developing hearing loss in men and women.

The mechanism of paracetamol-induced hearing loss was experimentally addressed in vitro [47]. The authors demonstrated that in the mouse auditory epithelium cell line, paracetamol and its metabolite NAPQI (*N*-acetyl-p-benzoquinoneimine) induce ototoxicity by causing oxidative stress as well as endoplasmic reticulum (ER) stress. These basic research results possibly explain the ototoxicity seen in people who regularly consume paracetamol. The question about usage of paracetamol and its frequency should be included in the surveys/questionnaires of patients with otologic and audiologic considerations.

Hydrocodone is a semi-synthetic opioid used for pain therapy and in common anti-cough medications. Hydrocodone is often prescribed in combination with paracetamol. In a report describing 12 patients with a history of hydrocodone overuse and progressive irreversible sensorineural hearing loss, the authors implicated nonresponsiveness of this type of hearing loss to corticosteroid therapy [48]. The authors reported that seven of eight patients who underwent consecutive cochlear implantation benefited from this type of auditory rehabilitation. Similar recent case report described a patient with unilateral hearing loss attributed to abuse of hydrocodone and paracetamol [49]. Also this patient was treated with cochlear implant.

The information delivered from the in vitro model with auditory epithelial cell line suggested that the combination of hydrocodone and paracetamol results in ototoxicity not due to hydrocodone but rather due to paracetamol [50]. The authors suggested that the contribution of hydrocodone to clinically seen ototoxicity may lay in hydrocodone assisting the addiction to the drug combination.

5. Methadone

Methadone is an opioid drug for treating pain. In addition, it is used for therapy of people addicted to opioids.

In the year 2014, about 7 million US citizens were abusing prescription drugs (source: National Center for Health Statistics). One of these drugs is methadone. Six recent case reports exposed an unknown before side effect of methadone abuse–the hearing loss [51–55]. The patients described in reports were young (age range 20–37) and were admitted to the hospitals because

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of methadone overuse. In all reported cases, the patients were deaf upon awakening (one perceived tinnitus), and in four of six cases, hearing loss was only temporary condition. The remaining two patients were unfortunately left with severe sensorineural hearing loss for the remaining observation time (2 and 9 months).

6. Immunosuppressant calcineurin inhibitors (cyclosporine A and tacrolimus)

Since the beginning of transplantology in the sixties, several people with incurable diseases of liver, kidney and other organs received the donor tissues as therapeutic procedure. This type of therapy is combined with an inevitable immune reaction against the *non-self* tissue. To prevent these reactions, immunosuppressants are used. Among them, cyclosporine A and tacrolimus (FK506) are commonly used to prevent graft rejection reaction. Both drugs decrease in various ways the activation of lymphocytes T and thus inhibit the graft rejection process. The immunosuppressants must be taken continuously.

Rifai et al. [56] performed a large study involving 521 liver transplant patients. The study was based on self-reported hearing loss and showed that of 521 individuals, 141 (27%) developed hearing loss following transplantation, particularly in those patients who were receiving tacrolimus as principal immunosuppression. This study was followed by recent trial, where instead of self-reported hearing loss, audiometric measurements were performed [57]. Of 70 liver transplant patients included in that study, 32 reported hearing loss and tinnitus following the transplantation. The types of hearing loss included sudden hearing loss and progressive hearing loss, which developed more than 3 years after transplantation. Audiometry confirmed the patients' reports and identified 12 patients with mild, 28 with moderate and 25 with severe hearing loss following the transplantation. The association between tacrolimus and hearing loss was seen again in this study.

Another group of transplant patients is the renal transplant group. Kidney transplantation is a surgical procedure performed since the mid-fifties last century; however, postsurgical survival was very low, because of the graft rejection [58]. The introduction of cyclosporine A in the eighties significantly improved the post-transplant survival rate but brought another type of problems, namely adverse reactions such as hearing loss. Renal patients are known to often have hearing impairments [59], and it was shown that the renal transplantation restores the hearing abilities, when measured 1 year after surgery. However, some renal transplant patients who are on a long-term immunosuppressant therapy such as cyclosporine A or tacrolimus develop hearing disabilities including sudden sensorineural hearing loss [60–62] or a progressive hearing loss [63].

Particularly, worrying tendency is seen among the pediatric renal transplant patients. A prospective study of 27 children (mean age 14) with normal hearing prior to kidney transplantation determined after a mean follow-up of 30 months that 17 children developed sensorineural hearing loss [60]. Two of 17 children were diagnosed with sudden hearing loss and the rest of the group with a progressive bilateral hearing loss.

It is likely that the ototoxic effect of immunosuppressants depends on the length of time of intake. Groups studying noise-induced hearing loss have successfully used cyclosporine A and tacrolimus to protect the auditory epithelium in mice from the noise-induced injury [64]. However, the dosage was single and not–like in the case of transplant patients–years long.

The treatment of hearing impairment occurring in organ transplant recipients includes hearing aids and cochlear implantation [65]. However, one should not ignore the fact that these patients are immunocompromised, and therefore, the risk of wound infection after CI should be taken under consideration during postsurgical management.

7. Mitochondrial toxicity: common denominator of ototoxic drugs

The auditory system requires a lot of energy produced in mitochondria [66–69]. Mitochondrial pathologies induced by genetic mutations are often associated with hearing loss [70–72]. Similarly, substances known to damage mitochondria such as aminoglycosides or cisplatin are known as ototoxic and contribute significantly to the hearing loss and tinnitus [73].

The substances listed in the present chapter can all damage the mitochondria. The damaging mechanism varies, and for instance, IFN-alpha impairs the transcription of mitochondrial DNA, whereas nucleoside analogues impair the replication of mitochondrial DNA [74]. In agreement with this, severe mitochondrial toxicity manifested by hyperlactatemia and pancreatitis was described in some cases involving patients with HIV/hepatitis C virus treated with pegylated interferon and ribavirin [75]. Paracetamol was also shown to have negative effect on mitochondria by inducing overproduction of reactive oxygen species (ROS) and inducing endoplasmic reticulum stress [47, 76]. Methadone was shown to impair synthesis of mitochondrial ATP leading to bioenergetics crisis of the affected organism [77]. The reverse transcriptase inhibitors used to slow down the replication of HIV virus were likewise demonstrated to induce mitochondrial toxicity [78, 79]. Lastly, cyclosporine A was shown to inhibit adenine nucleotide net transport into the mitochondria [80], whereas tacrolimus was associated with decreasing the levels of oxidative phosphorylation in mitochondria [81].

Since the negative effect of various drugs on mitochondria likely results in a damage of hearing, it is plausible that the mitochondria-supporting substances (such as coenzyme Q10, vitamin B12 with folic acid, sirtuin and many others) given as auxiliary therapy could protect the sense of hearing in patients with hepatitis, HIV, transplant patients or painkiller or PDE5 inhibitor users. In fact, targeting mitochondria is becoming increasingly popular [82], and there were some successful attempts in treatment of hearing conditions using mitochondrial supplements [83–89].

8. Conclusions

The appearance of new drugs to treat ever more conditions is an inevitable and welcomed progress of medical and pharmaceutical sciences. However, assuring the drug safety in terms

of hearing disability is difficult, and it often requires very long and regular intake periods, which are outside of regular phase I, II or III clinical trials. As for the duration of phase IV (the postmarketing surveillance trials), which is usually set for 2 years, perhaps it could be extended specifically for the monitoring of audiological conditions.

The ototoxicity of prescription or over-the-counter drugs is a global problem. Collaboration between audiologists or otologists and other healthcare providers is necessary to protect the patient's auditory health. Auditory consultations ought to be a routine during the treatment of patients with viral hepatitis C or B receiving interferons and ribavirin or HIV-positive individuals taking anti-reverse transcriptase drug cocktail. Moreover, patients undergoing solid organ transplantation should be audiologically monitored. The option of audiological care for children treated for any of the above infectious diseases or undergoing transplantation should be presented to their parents. Lastly, frequent users of painkillers and recreational drugs should be informed about the risks of the medications they are reaching for every day.

During the unavoidable drug therapies, preventive means such as mitochondrial protection and supplementation during the drug treatment and audiological monitoring as well as fitting the patients with hearing aids or cochlear implants, could help to keep the hearing healthy or at least to restore it to some degree.

The good condition of hearing is as important as that of heart, lung or other organs. Informing the community about ototoxicity and keeping up to date with the case reports and other scientific communications may help to save the sense of hearing.

Glossary of terms

Cyclosporine A	Fungal metabolite that suppresses immune reaction. It inhibits the activation of lymphocytes T by binding to cyclophilin and inhibiting calcineurin
Endocochlear potential	Voltage of +80mV in the scala media, generated by the stria vascularis, essential for the auditory transduction
Interferon (IFN)-alpha	Small signaling protein produced and released mainly by white blood cells in response to viral infection
Interferon (IFN)-beta	Small signaling protein produced and released mainly by fibroblasts in response to viral infection
Intratympanic injections	Injections through the eardrum into the middle ear cavity
Mycobacterium tuberculosis	Infectious microorganism causing tuberculosis
Nucleoside	Glycosylamine (e.g., cytidine, uridine, adenosine, guanosine or thymidine), primary DNA or RNA molecule. Also known as nucleotide without phosphate group

Phosphodiesterase-5 (PDE5)	Enzyme that catalyzes the hydrolysis of cyclic GMP and regulates tonus of smooth muscle cells
PDE5i	Phosphodiesterase-5 inhibitors
Polyethylene glycol (PEG)	Polymer of ethylene oxide. PEG can be bound to proteins, therefore slowing their decay time in the body
Protease inhibitor	Inhibitor of enzymes that degrade proteins. Viral proteases are essential for viruses to complete their life cycle
Reverse transcriptase (RT)	Enzyme that synthesizes DNA using as a template RNA, a process called reverse transcription. This process is specific for viral replication and is used for instance by HIV virus
Tacrolimus (FK-506)	Bacterial derivative isolated from Streptomyces tsukubaensis. Tacrolimus inhibits activation of lymphocytes T via inhibiting calcineurin. Similar but not identical in action to cyclosporine A

Author details

Agnieszka J. Szczepek

Address all correspondence to: agnes.szczepek@charite.de

ORL Research Laboratory, Department of ORL, Head and Neck Surgery, Charité University Hospital, Berlin, Germany

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