

## Ototoxicity-the Hidden Menace. Part I: Lives in Upheaval

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*EDITOR'S NOTE - Although most audiologists are familiar with ototoxicity, this article is an in-depth, patient-friendly review of the possible signs, symptoms, outcomes and issues. This article is written with the patient as the intended audience. Please note, there are two parts to this article. The second part will be available on Audiology Online December 15, 2003. Please feel free to read, review, download and print copies for your waiting room! I encourage professionals and patients to order the brand-new second edition of Ototoxic Drugs Exposed by Neil Bauman from his web site at <http://www.hearinglosshelp.com/ototoxicdrugbook.htm>>*

"Lynn's" passion was flying. She loved her job as a flight attendant. One day she noticed an ingrown toenail. Within a few days it became infected. The **Gentamicin**<sup>1</sup> her doctor prescribed killed the infection. It also killed the balance system in her ears. Ever since that fateful day in 1994, Lynn has not been able to work or fly. Without warning, an ototoxic drug turned her world upside down.

An ototoxic drug flipped "Ruby's" life upside down too. She explains: "I cannot drive any more. I had to quit my job as it was an hour's drive away. My mental status is now "foggy" at best. I cannot walk in the dark. My life has changed drastically."

"Bert" lost much of his hearing after taking **Doxycycline** for a urinary tract infection. "Eunice" told me that just taking the **Amitriptyline** her doctor prescribed for her resulted in "screaming tinnitus."

"Jonathan" described how he lost hearing in one ear after he took a course of **Erythromycin**. In addition, he experienced hyperacusis, balance problems and "horrific bilateral tinnitus." "Jonathan's" condition appears to be permanent—as this happened five years ago.

Peggy told me, "I was given **Atenolol** for some little irregular heart beats. Within a few days my perfectly normal ears started to give me all kinds of noise, roaring and muffledness. Within a week, I woke up one morning stone cold deaf in one ear."

In an email to me, "Sam" told how his doctor had prescribed an ointment containing **Tobramycin** for a sty on his left eyelid. He wrote, "I started using the cream on my left eyelid on Tuesday. At 8:30 the next morning, I lost the hearing in my left ear." In "Sam's" case, the **Tobramycin** apparently caused sudden hearing loss just 19 hours later—and this was only from using an ointment on his eyelid!

I wish I could say these are only a few isolated incidents, but I'd be lying if I did so. The truth is—side effects of ototoxic drugs are more common than people (doctor's included) imagine. Each year, the side effects of ototoxic drugs disrupt millions of people's lives and leave a trail of upheaval in their wake.

It is not just drugs taken for chemotherapy and life-threatening infections that cause ototoxic reactions, but the little unexpected everyday things too—an ingrown toenail, a sty on your eye, an irregular heartbeat, high blood pressure, and on and on it goes. Whether the ototoxic side effects result from taking an ototoxic drug for a life-threatening malady or for a relatively minor disorder, the results are the same—lives turned upside down.

Scary? You bet it is. Obviously, it's about time we became aware of what drugs are doing to our ears and learn to make wise decisions regarding them.

### **What Is Ototoxicity?**

To many doctors, ototoxicity just means hearing loss or tinnitus. Others consider only drug side effects that affect the inner ear as being ototoxic. However, *Stedman's Medical Dictionary*<sup>11</sup> defines ototoxicity as the "property of being injurious to the ear." Therefore, any side effect of a drug that damages our ears in any way is ototoxic whether it damages the outer, middle or inner ear.

### **How Common Are Ototoxic Side Effects?**

How common are ototoxic side effects? The short answer is, "No one really knows." We apparently only see (and record) the tip of the iceberg. For extremely ototoxic drugs such as **Cisplatin** (used in the treatment of cancer), virtually everyone that takes this drug ends up with hearing loss. According to some researchers, not a single person escapes its ravages—100% of the people taking **Cisplatin** damage their ears.<sup>5</sup> The resulting hearing loss "is usually irreversible (permanent)."<sup>8</sup>

Another very ototoxic class of drugs are the Aminoglycoside antibiotics. Researchers estimate that between one and four million Americans receive Aminoglycoside antibiotics (such as **Gentamicin**, **Neomycin**, **Tobramycin**) each year.<sup>7</sup> According to one study, a person has a 25-30% chance of incurring hearing loss from taking any of the Aminoglycosides.<sup>9</sup> Another study pegs the figure at 63%.<sup>5</sup>

This means that between 250,000 and 1,200,000 people (and maybe as high as 2,520,000 people) in the USA incur hearing losses each year from taking just this one class of drugs. Add to these figures the untold numbers of people who experience other side effects from taking these same drugs—such as tinnitus, dizziness, vertigo and numerous other cochlear and vestibular (balance) problems—and you have a figure of alarming proportions. It is even more alarming when you realize we are just talking about a handful of ototoxic drugs in 2 of the more than 150 classes of ototoxic drugs!

### **Ototoxic Drugs are Everywhere!**

There are at least 743 drugs that are known to be ototoxic.<sup>4</sup> Here are just 84 of them. This

gives an inkling of just how all-pervading ototoxic substances are in the medications we take without having a clue that these drugs may be harming our ears.

- ACE inhibitors such as **Enalapril** (*Vasotec*),<sup>2</sup> **Moexipril** (*Univasc*), **Ramipril** (*Altace*)
- Acetic acids such as **Diclofenac** (*Voltaren*), **Etodolac** (*Lodine*), **Indomethacin** (*Indocin*), **Ketorolac** (*Toradol*)
- Alpha blockers such as **Doxazosin** (*Cardura*)
- Aminoglycosides such as **Amikacin** (*Amikin*), **Gentamicin** (*Garamycin*), **Kanamycin** (*Kantrex*), **Neomycin** (*Neosporin*), **Netilmicin** (*Netromycin*), **Streptomycin**, **Tobramycin** (*Tobradex*)
- Angiotensin-2-receptor antagonists such as **Eprosartan** (*Teveten*), **Irbesartan** (*Avapro*)
- Anti-arrhythmic drugs such as **Flecainide** (*Tambocor*), **Propafenone** (*Rythmol*), **Quinidine** (*Cardioquin*), **Tocainide** (*Tonocard*)
- Anti-cancer drugs such as **Buserelin** (*Suprefact*), **Carboplatin** (*Paraplatin*), **Cisplatin** (*Platinol*), **Vinblastine** (*Velban*), **Vincristine** (*Oncovin*)
- Anti-convulsant drugs such as **Carbamazepine** (*Tegretol*), **Divalproex** (*Depakote*), **Gabapentin** (*Neurontin*), **Tiagabine** (*Gabitril*), **Valproic acid** (*Depakene*)
- Anti-malarial drugs such as **Chloroquine** (*Aralen*), **Mefloquine** (*Lariam*), **Quinine** (*Legatrin*)
- Anti-retroviral protease inhibitors such as **Cidofovir** (*Vistide*), **Ganciclovir** (*Cytovene*), **Ritonavir** (*Norvir*)
- Benzodiazepines such as **Diazepam** (*Valium*), **Estazolam** (*ProSom*), **Midazolam** (*Versed*)
- Beta-blockers such as **Atenolol** (*Tenormin*), **Betaxolol** (*Betoptic*), **Metoprolol** (*Lopressor*)
- Bicyclic anti-depressants such as **Venlafaxine** (*Effexor*)
- Calcium-channel-blockers such as **Diltiazem** (*Cardizem*), **Nifedipine** (*Adalat*), **Nisoldipine** (*Sular*)
- Cox-2 inhibitors such as **Celecoxib** (*Celebrex*), **Rofecoxib** (*Vioxx*)
- H1-blockers such as **Cetirizine** (*Zyrtec*), **Fexofenadine** (*Allegra*)

- Immunosuppressant drugs such as **Cyclosporine** (*Neoral*), **Muromonab-CD3** (*Orthoclone OKT3*), **Tacrolimus** (*Prograf*)
- Loop diuretics such as **Ethacrynic acid** (*Edecrin*), **Furosemide** (*Lasix*), **Torsemide** (*Demadex*)
- Macrolide antibiotics such as **Clarithromycin** (*Biaxin*), **Erythromycin** (*Eryc*)
- Opiate agonist drugs such as **Codeine** (*Codeine Contin*), **Hydrocodone** (*Vicodin*), **Tramadol** (*Ultram*)
- Propionic acids such as **Flurbiprofen** (*Ansaid*), **Ibuprofen** (*Motrin*), **Naproxen** (*Anaprox*)
- Proton pump inhibitors such as **Esomeprazole** (*Nexium*), **Lansoprazole** (*Prevacid*), **Rabeprazole** (*Aciphex*)
- Quinolones such as **Ciprofloxacin** (*Cipro*), **Ofloxacin** (*Floxin*), **Trovafloxacin** (*Trovan*)
- Salicylates such as **Aspirin**, **Mesalamine** (*Asacol*), **Olanzapine** (*Zyprexa*)
- Selective serotonin reuptake inhibitors (SSRIs) such as **Fluoxetine** (*Prozac*), **Fluvoxamine** (*Luvox*), **Sertraline** (*Zoloft*)
- Serotonin-receptor agonists such as **Almotriptan** (*Axert*), **Naratriptan** (*Amerge*), **Sumatriptan** (*Imitrex*)
- Thiazides such as **Bendroflumethiazide** (*Corzide*), **Indapamide** (*Lozol*)
- Tricyclic anti-depressants such as **Amitriptyline** (*Elavil*), **Clomipramine** (*Anafranil*)

## Ototoxic Side Effects

Ototoxic side effects can damage our ears in many different ways. You may experience one, several or no side effects from taking any given drug. The average ototoxic drug exhibits about 3.5 ototoxic symptoms.<sup>4</sup> Here are a number of the ototoxic side effects you could experience.

When you know which ototoxic side effects can occur, you can watch for them. If they do occur, immediately contact your physician, stop taking the offending drug (with your doctor's consent—of course) to try to limit the damage to your ears.

### 1. Cochlear side effects

- **Tinnitus:** Tinnitus, commonly called "ringing in the ears," is the number one indicator that you may be damaging your ears from an ototoxic drug. At least 447

drugs are known to cause tinnitus.<sup>4</sup> Tinnitus can manifest itself as a wide variety of sounds. It may be a ringing, roaring, beating, clicking, banging, buzzing, hissing, humming, blowing, chirping, clanging, sizzling, whooshing, rumbling, whistling or dreadful shrieking noise in your head. It may also sound like rushing water, radio static, breaking glass, bells ringing, owls hooting or chainsaws running.<sup>3</sup>

- **Hearing loss:** More than 230 drugs are known to cause hearing loss.<sup>4</sup> Hearing loss can range from mild to profound and may be temporary or permanent. One of the insidious things about ototoxic drugs is they generally first destroy hearing in the very high frequencies which are not normally tested (those above 8,000 Hz). Thus, you're not even aware you are losing your hearing until it is too late to do anything about it.
- **Distorted hearing:** Some drugs, instead of causing hearing loss (or in addition to causing hearing loss), cause hearing to be distorted so we do not understand some (or much) of what we are hearing.
- **Hyperacusis:** Hyperacusis is a condition where normal sounds are perceived as being much too loud. It is as though the body's internal volume control is stuck on "high." At least 38 drugs can cause this condition.<sup>4</sup>
- **Feelings of fullness in your ears:** You can experience this feeling for a few reasons. One, because your ears really are blocked by a middle ear infection or by earwax. Two, because your ears **feel** "blocked" because of sudden hearing loss. Three, exposure to loud sounds can result in a feeling of "fullness" too.
- **Auditory hallucinations:** At least 8 drugs can cause you to hear phantom sounds—voices and music that are not there. Another 165 drugs can cause hallucinations, some of which may be of the auditory variety.<sup>4</sup> Most of these hallucinations seem to be the result of a damaged auditory system rather than the effects of a mental illness.

## 2. Vestibular Side Effects

- **Dizziness:** Dizziness is the most common ototoxic symptom. At least 588 drugs have this ototoxic side effect.<sup>4</sup>
- **Vertigo:** Vertigo is the perception of movement (normally a spinning sensation) when the body is really not moving. At least 432 drugs are known to cause vertigo.<sup>4</sup>
- **Ataxia:** Ataxia is the loss of your ability to coordinate your muscles properly and can be a result of a damaged vestibular system. As a result you may walk with a staggering gait, just as though you were drunk. At least 288 drugs can cause this side effect.<sup>4</sup>

- **Nystagmus:** Nystagmus is abnormal rapid rhythmic back-and-forth involuntary eye movement, usually from side to side. Although technically an eye problem, it fundamentally is the result of a damaged vestibular system. At least 102 drugs can cause this side effect.<sup>4</sup>
- **Labyrinthitis:** Labyrinthitis is a catch-all term that simply means something is wrong in your inner ear (cochlear and vestibular systems).
- **Loss of balance/equilibrium disorder:** Some drugs cause a person to lose their balance. These terms too, are mostly catch-alls for various kinds of balance conditions.
- **Oscillopsia:** Oscillopsia is "bouncing vision." This is the result of damage to the vestibular system such that it no longer works together as the vestibulo-ocular reflex. Oscillopsia can result when your vestibular system in both ears is severely damaged.
- **Emotional problems:** When you lose much of your sense of balance, emotional problems such as anxiety, frustration, anger and depression can surface.<sup>7</sup> Your feelings of self-confidence and self-esteem may plummet.
- **Fatigue:** Damage to the vestibular system can result in exhaustion, because you now have to consciously work at maintaining your balance.
- **Memory problems:** Memory problems can result because areas of your brain that were previously used for thought and memory, must constantly work on keeping you balanced. As a result, you may grope for words, forget what was just said, be easily distracted or have trouble concentrating.
- **Muscular aches and pains:** Another seemingly-unlikely result of vestibular ototoxicity are muscle pains due to failure of the vestibulo-spinal reflex (the reflex dictating automatic muscle changes in response to changing movement). If the reflex fails, you have to consciously control it. You may make your muscles rigid as you strain to keep your balance.
- **Nausea:** Nausea is a relatively common side effect of vestibular damage that results from your brain's confusion over vestibular sensory inputs.
- **Visual problems:** A host of visual problems can result if the vestibulo-ocular reflex (the reflex that stabilizes your eyes in space) is damaged. As a result, you may have trouble reading since everything seems blurry or fuzzy. You may have trouble focusing your eyes—particularly on moving or distant objects.<sup>6</sup>
- **Vomiting:** Vomiting is a common result of a damaged vestibular system. Often vomiting and vertigo go together.

- **Vague feelings of unease:** Sometimes you can't put your finger on exactly what is wrong, but you feel vaguely uneasy. You may feel that things seem wrong or unreal.<sup>7</sup> This too, can be a result of a damaged vestibular system.

### 3. Central Nervous System (CNS) Side Effects

- **Central auditory processing disorder:** Sounds may enter our ears and be processed correctly, but these sound signals may be delayed or scrambled after they leave our inner ears. This scrambling can occur as the sound signals are processed by the neuronal networks that make up our auditory nerves, or in various parts of our brains. When this processed sound reaches the conscious levels in our brains where we "hear," we may hear a bunch of gibberish. This is known as a central auditory processing disorder. Several ototoxic drugs/chemicals have this effect.

### 4. Outer/Middle Ear Side Effects

- **Ceruminosis:** Some drugs cause excessive ear wax production. This excess wax can block our ear canals and cause temporary hearing loss.
- **Ear pain:** Medically called otalgia, ear pain is typically the result of middle ear infections. 154 drugs have ear pain associated with their use.<sup>4</sup>
- **Otitis externa; O. media:** Otitis is typically an opportunistic infection of the outer (O. externa) or middle (O. media) ear. Many of the drugs listed as having otitis as an ototoxic side effect do not directly cause these conditions. Rather, these infections come in and take over when an opportunity presents itself—i.e. an ototoxic antibiotic killing off the "good bacteria" in the ear canal, leaving it wide open to an opportunistic invasion of "bad bacteria." 138 drugs are associated with otitis.<sup>4</sup>

### Risk Factors

Some people take ototoxic drugs with seeming impunity. Others take one little dose, and wham—there goes their ears. Why?

The short answer is that we are all different. Each person (patients and professionals) is a unique biological case study! No two are exactly the same. Therefore, it should be no surprise that we vary in our sensitivity to ototoxic drugs.

Researchers have identified a number of factors that increase the risk of our having an ototoxic reaction when taking certain drugs. Here are 20 of the risk factors (in no particular order of importance).

1. You are very young—including unborn children.
2. You are a senior (over 60 years).

3. You have certain hereditary (genetic) factors that make you more susceptible than the general population. This is particularly true if you take Aminoglycoside antibiotics.
4. You already have a sensorineural hearing loss, balance problems or some other form of pre-existing ear damage.<sup>12</sup>
5. You have had previous ear damage (hearing loss) from exposure to excessive noise.
6. You have problems with your kidneys. For some reason, people with kidney problems have an unusually high incidence of hearing loss, even without drug use.<sup>10</sup>
7. You are extremely sensitive to drugs or have a low tolerance for drugs.
8. You have had ototoxic reactions to drugs in the past. Not only does the risk increase, but the resulting ototoxic damage has a tendency to be more severe and is more likely to be permanent.<sup>7</sup>
9. You have previously used ototoxic drugs, or you have taken repeated courses of the same ototoxic drug.
10. You have taken certain drugs for a long time—especially if you have taken a drug for longer than the manufacturer recommended.
11. You can be at higher risk if an ototoxic drug is not administered properly—i.e. larger than recommended dose, higher than recommended cumulative dose, faster dose than recommended (injection or intravenous).<sup>7</sup>
12. You have been given an inappropriate dose—i.e. a child given an adult dose, or an overweight person given a dose based on total weight rather than on lean body weight (especially true if taking an Aminoglycoside antibiotic).<sup>7</sup>
13. You are dehydrated.
14. You have taken ototoxic Diuretics at the same time as other ototoxic drugs or if you have used or are using two or more ototoxic and/or nephrotoxic (toxic to the kidneys) drugs at the same time.
15. You have had previous ear infections.
16. You are generally in poor health.
17. You have abnormal laboratory values such as reductions in serum albumin, serum red blood cells, hematocrit, hemoglobin or you have rising serum creatinine levels.<sup>7</sup>



18. 18. You have had radiation treatments on your head or ear.<sup>6</sup>
19. 19. You have bacteremia (bacteria in the bloodstream).<sup>7</sup>
20. 20. You have either eye or proprioceptive (balance) problems. This increases the chances that you will have a more serious result on your life-style if vestibular ototoxicity does occur.<sup>7</sup>

### **Reduce The Risk—Here's How**

You cannot do anything about certain ototoxic risk factors such as your age or your genetic makeup. However, there are still some things you (and your doctor) can do to lessen your risk of having an ototoxic reaction from taking certain drugs.

Here are some things you and your doctor can do.

1. Be aware of the early warning signs of ototoxicity. The are (in order of frequency): you feel dizzy; your ears begin ringing (tinnitus); your existing tinnitus gets worse or you hear a new kind of tinnitus sound; you feel pressure in your ears (unless you have a head cold); your hearing gets worse or begins fluctuating; or you develop vertigo (spinning sensation).
2. Tell your doctor you are hard of hearing, especially if you have a sensorineural hearing loss and/or suffer from balance problems. Also, let him know if you have tinnitus.
3. Always discuss possible side effects with your doctor before you begin a new medication.
4. Follow your doctor's dosage instructions exactly. At the same time, make sure your doctor does not exceed the drug manufacturer's dosage instructions when he prescribes drugs for you.
5. Use the same pharmacy for all your prescriptions so they will know all the drugs you are taking. That way they can advise you of any known dangerous drug combinations.
6. Always read the labels on over-the-counter medications and particularly watch for ototoxic side effects.
7. Drink plenty of fluids so you don't get dehydrated. This is especially important if you have a fever or are taking loop diuretics.
8. If you have kidney problems, have your health care professionals carefully monitor your kidney function and report abnormalities immediately. Your doctor needs to know how well your kidneys are working before he prescribes various medications.

9. Avoid taking multiple ototoxic drugs at the same time.
10. Avoid noisy environments for at least 6 months after you have completed a course of an Aminoglycoside antibiotic or platinum compound such as **Cisplatin**.<sup>8</sup>
11. If you are beginning treatment with an ototoxic drug such as any of the Aminoglycoside antibiotics, Loop diuretics or platinum compounds such as **Cisplatin**, it is important that you have a baseline high-frequency audiogram done before you begin treatment and then serial high-frequency audiograms (testing those frequencies above 8,000 Hz) during and after drug therapy.
12. If you have had vestibular (balance) problems from taking any drugs, be very careful not to damage your vestibular system further by taking drugs known to damage your vestibular system.

When you are aware of the many drugs that can damage your ears and the many risk factors that can make you even more susceptible to ototoxic side effects than the general population, you can take steps to protect your precious ears.

You will then be in the position to take control and make informed decisions about your health care. For example, "Joan" takes **Celecoxib** for her arthritis. When she takes it, her tinnitus gets louder, but her arthritis problems improve. She chooses the tinnitus over the arthritis pain. That is her choice and she is content to live with it.

"Harold," on the other hand, began taking **Amitriptyline** and soon noticed he had severe tinnitus. He didn't like this one bit and wrote to me for help. I suggested the **Amitriptyline** may be causing his tinnitus. With his doctor's permission, he stopped taking the drug. Twelve days later, he joyfully reported that his tinnitus went away. That was his choice. He is happy he made it.

When it comes to the health of your ears, you, too, have a choice. Use it wisely.

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If you would like to learn more about the 743 ototoxic drugs, 30 herbs and 148 chemicals and how you can help protect your ears from their specific side effects, order your copy of the brand-new second edition of **Ototoxic Drugs Exposed** by Neil Bauman from his web site at <http://www.hearinglosshelp.com/ototoxicdrugbook.htm>.

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## Notes

<sup>1</sup> In this paper, drug classes are in small capitals (ACE INHIBITORS), generic drug names are in bold (Enalapril) and brand names are in italics (Vasotec).

<sup>2</sup> The brand names listed here are neither more or less ototoxic than any brands of this same generic drug that are not listed. I have simply chosen, more or less at random, one brand as a representative of all the brands available for that generic drug.

## References

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## **Part Two: Ototoxicity and the Practice of Audiology**

Part One of this series presented an overview of the hundreds of ototoxic drugs currently available and how their potential side effects relating to hearing and balance turn countless lives upside down. Part One also detailed risk factors that predispose people to ototoxic effects and concluded with what individuals can do to reduce their risk.

In Part Two, we'll examine things you, as an audiologist, can do to help your patients when their ears "butt heads" with ototoxic substances.

### **Think "Drugs" When Assessing Hearing Loss**

As you know, when patients present for hearing evaluations, it is important to ask what medications they're taking. However, the importance of this questioning is not limited to a thorough and complete history. Rather, this knowledge may indeed impact their current status and future-based medical decision making.

If you look up their medications in *Ototoxic Drugs Exposed*,<sup>1</sup> you'll quickly get an idea as to what may be happening to their ears. If ototoxic side effects started (or increased) around the time they began taking certain drugs, the ototoxic "index of suspicion" is elevated, and indeed, their current medications may be damaging their ears.

Given an elevated index of suspicion, and armed with objective data, you might contact the physician and suggest that perhaps alternative, non-ototoxic alternative medications might be an option.

For example, suppose a patient comes to you with severe hyperacusis which is disrupting her life. What do you do? Do you immediately think of something like Hyperacusis Retraining Therapy, or do you think "drugs?"

I suggest as a first step—think "drugs."

When patients ask me what they can do about their hyperacusis, among the first questions I ask is, "What happened in your life just before the hyperacusis began? Did you start taking new medications or was there a change in the dose of existing medications?" I ask for a complete list of their medications and I look them up in *Ototoxic Drugs Exposed* to see if any of them are known to cause hyperacusis. If any of them are known to cause hyperacusis, I suggest to the patient that he/she contact the doctor to investigate alternative drugs with the same benefits, but without hyperacusis as a known side effect. In certain situations, I may communicate directly with the physician on these issues.

A psychiatrist explained that a patient of hers had several psychiatric problems, but the one thing bothering the patient above all else was severe hyperacusis. The patient had tried hyperacusis remedies without improvement. The psychiatrist asked me if there was anything that might help her patient.

My first reaction was to "think drugs." I asked what medications the patient was on and

what medications she had been on at the time the hyperacusis began. When I received the list of medications, I discovered that this patient was taking not just one, but three drugs known to cause hyperacusis! Of all the thousands of drugs on the market, only 38 are known to cause hyperacusis, yet this poor patient was taking three of them at the same time!

I suggested the psychiatrist consider taking the patient off those three particular medications (if medically possible) and then see whether the patient's hyperacusis was reduced or eliminated.

A man contacted me telling me he had severe tinnitus and he wanted to know if there was anything he could do about it. Instead of suggesting a tinnitus masker or Tinnitus Retraining Therapy (TRT) or other treatments, I immediately thought "drugs." I asked if he had started any new medications about the time his tinnitus began.

He told me his doctor had recently put him on **Amitriptyline**. I suggested he ask his doctor to change his medication, if possible, as **Amitriptyline** is known to cause tinnitus. A couple of weeks later, he wrote me again, saying that 12 days after he stopped taking the **Amitriptyline**, his tinnitus went away. Again, the solution was simple and effective. Think "drugs."

A woman contacted me as she was experiencing annoying tinnitus and increasing hearing loss. As is my custom, I thought "drugs." I discovered she had been self-medicating—taking large doses of **aspirin** each day for the nearly-constant headaches she often suffered.

I suggested to her that her hearing problems and her tinnitus were very likely a direct result of taking all that **aspirin**. She stopped taking **aspirin**. Six days later she wrote, "I have noticed that I am hearing better now. I have the TV volume set at level 18 instead of the usual 24. The ringing in my ears is still there but it is not as bad." Three days later she added, "Today when someone was talking behind me, I heard every word he said. My hearing still isn't perfect, but it is better than it was."

The people in the above examples didn't need expensive or extensive therapy or hearing aids. What they really needed was someone to help them see that they were damaging their ears due to medications they were taking. In many cases, you'll be able to help your patients more when you first think "drugs."

### **While You Are Thinking "Drugs," Think "Chemicals" Too**

It is not only ototoxic drugs that damage our ears, there are at least 148 ototoxic chemicals that also give us grief.<sup>1</sup>

Two of the more ototoxic classes of chemicals are the organic solvents and the heavy metals.

There are a number of organic solvents. Some of them are **benzene, benzyl alcohol, butyl alcohol, carbon disulfide, carbon tetrachloride, heptane, hexane, styrene, toluene, trichloroethylene** and **xylene**. Ototoxic heavy metals include **arsenic, cobalt, lead, manganese, mercury** and **trimethyltin**.

Most people likely have a number of ototoxic chemicals in or around their homes. Some of these ototoxic chemicals include adhesives, auto emissions, fungicides, glues, grease and spot removers, insecticides, insulation, lacquers, liquid correction fluid, organic solvents, paint, paint thinners, resins, room deodorizers, rug cleaners, spray paint, varnishes and wood preservatives to name a few.<sup>13, 14</sup>

In addition, people may be exposed to ototoxic chemicals if they work in one of the many manufacturing plants and factories that use organic solvents or heavy metals. Such processes as electroplating, shoe manufacturing, dry cleaning, cold vulcanization, electronic battery manufacture and polyvinyl chloride manufacturing all use various ototoxic chemicals.<sup>14</sup>

Further, the pollutants in the air can also hurt peoples' ears. Depending on the type and severity of the air pollution, people can end up with hearing loss, balance problems or other damage to their ears.<sup>2</sup>

Most people probably think of air pollution as occurring outside. However, dangerous air pollution also resides within homes, offices and factories. Many of the indoor pollutants are organic solvents. When people inhale fumes from these solvents, they slowly but surely damage their ears.

One study of workers in a rubber factory revealed 47% had subclinical abnormalities in the auditory pathways and in their brainstems, due to solvents used in manufacturing rubber.<sup>16</sup> One patient lost her hearing resulting from several years of using spray varnish in her garage without adequate ventilation. **Toluene** in the varnish was the culprit.

Sometimes, ototoxic damage from organic solvents is obvious—such as when it results in massive hearing loss or roaring tinnitus. However, in other cases (see above study) results can be insidious and subtle, presenting as impaired central auditory processing. Even though the chemical hasn't caused reduced "hearing" as might be expected on an audiogram, the person affected can't understand everything they hear.

A bit of probing may reveal that hearing loss is the result of exposure to an ototoxic chemical where you least expect to find it. Therefore, in addition to thinking "drugs," also think "chemicals."

### **Drug Interactions and Ears**

Little is known about how ototoxic drugs adversely affect our ears. Dramatically less is known about ototoxic side effects when two or more ototoxic drugs are consumed at the same time. However, some interesting (and important) things have come to light in recent

years.

When a person takes two or more ototoxic drugs at the same time, or one immediately following the other, there are two likely outcomes. The ototoxic effects of each drug can either be additive, or the ototoxic effects can be synergistic.

In the first case, the total effect on the ears will be the sum of the effects of each drug as if they were taken separately. For example, if one ototoxic drug causes 2 "units" of damage and the second drug causes 3 "units" of damage, the resulting damage on the ear would be 5 "units" ( $2 + 3 = 5$ ). This is the additive effect.

However, with some drug combinations, using the same example above, the result is not 5 "units" of damage as you might expect, but a larger number—say 10 "units" of damage. This represents a synergistic effect. With synergistic effects, the resulting damage is always greater than the sum of the damage of each individual drug.

To protect ears as much as possible, people should not take multiple ototoxic drugs at the same time, especially if they are known to have synergistic ototoxic effects.

Researchers have discovered that the order a person takes certain ototoxic drugs can make an enormous difference as to whether they have much of a resulting hearing loss or not. With some drug combinations, if you take the drugs sequentially, and not simultaneously, you can avoid the synergistic effect.

For example, in one medical treatment, doctors put their patients on two drugs, a Loop diuretic (e.g., **Furosemide**) and an Aminoglycoside antibiotic (e.g., **Tobramycin**). If the patient completes the course of the Loop diuretic **before** he begins the Aminoglycoside antibiotic, the resulting hearing loss from these two drugs is additive. However, if the patient takes both drugs simultaneously or if the Aminoglycoside antibiotic is administered first, followed by the Loop diuretic—the two drugs act synergistically to significantly damage the patient's ears.<sup>25</sup>

Not only do certain ototoxic drugs react synergistically with each other, but they have another nefarious characteristic. Their ototoxic side effects can react synergistically with noise.

Certain ototoxic drugs when taken "normally" can result in a certain degree of hearing loss. However, if they are being taken while the patient is exposed to loud noise, the noise combines synergistically with the ototoxic side effects of the drug to cause even greater hearing loss than might otherwise be expected.

Some of the drugs that have this vicious effect include **aspirin**,<sup>20</sup> the anti-cancer drug **Cisplatin**,<sup>22</sup> the microbial antibiotic **Chloramphenicol**<sup>3</sup> and Aminoglycoside antibiotics such as **Gentamicin**<sup>12</sup> and **Kanamycin**.<sup>23</sup>

This same synergistic effect on hearing loss between the ototoxic side effects of certain

drugs and noise also occurs between certain chemicals and noise. Chemicals that make our ears more prone to hearing loss as a result of noise include organic solvents such as **carbon disulfide**, **dinitrobenzene**, **styrene**, **trichloroethylene**, **toluene** and **xylene** as well as the asphyxiant **carbon monoxide** and the heavy metal **lead**.<sup>4, 10, 17, 26</sup>

Other chemicals with this same nefarious characteristic include **arsenic**, **butyl alcohol**, **butyl nitrite**, **heptane**, **hexane**, **manganese**, **mercury** and **trimethyltin**.<sup>19</sup> This apparently is just the tip of the iceberg. Suspicion is already cast on **carbon tetrachloride**, various other metals and asphyxiants.<sup>17, 20</sup>

Just how pronounced is this synergistic effect? Sometimes the results can be dramatic! In a study of Brazilian workers, those exposed to both noise and **toluene** had a 53% incidence of hearing loss. In contrast, those exposed to noise alone had a 26% incidence rate while the control group had an incidence rate of only 8%. When these results were adjusted for age, they showed that noise exposure increases the risk of hearing loss by 4.6 times. When the noise was combined with exposure to **toluene**, the risk jumped a whopping 27.5 times!<sup>21</sup>

In another study, workers were grouped into one of four groups—those exposed to both noise and **toluene**, those exposed to **toluene** alone, those exposed to noise alone, and those not exposed to either **toluene** or noise (the control group). The hearing loss of those exposed to noise alone was 4 times greater than the control group; the hearing loss of those exposed to **toluene** alone was 5 times greater; and the hearing loss of those exposed to both noise and **toluene** was 11 times greater!<sup>17</sup>

One treacherous result of certain ototoxic drugs combined with noise is something you'd probably never suspect—the length of time a person's ears are still susceptible to the synergistic effects of ototoxic drugs and noise—**after** the drug has been discontinued.

If you tell a person not to take certain drugs while he is exposed to noise, he might think you are referring to the days he is actually taking the drug therapy. Surprise! Not true! A person has to avoid noise for much, much longer.

When a person takes Aminoglycoside antibiotics or platinum anti-cancer drugs, such as **Cisplatin**, they are quickly transported to his inner ears. The problem is that, once there, these drugs persist in the inner-ear fluids long after they have disappeared from the bloodstream,<sup>11</sup> not just for a few days, but for several weeks to several months,<sup>15</sup> and up to a year later!

During the time these drugs are present in peoples' inner ear fluids, they can be damaging their ears. More importantly, during this time, their ears are especially susceptible to the synergistic effects of loud noise.<sup>15</sup> This means that if people have taken Aminoglycoside antibiotics or **Cisplatin** and are now finished with this drug therapy, their ears are still in danger of even more hearing loss if they expose them to loud noise any time in the next few months or more, depending on their specific body chemistry.



This has important implications for the audiologist treating hearing aid patients with hearing aids and other amplification systems. Dr. James Kalkanis, M.D., recommends setting the gain and maximum power output (MPO) as low as possible in order to protect your patients' ears while their ears are very sensitive to the effects of noise, secondary to ototoxic medications. If a patient already wears hearing aids, you should instruct him to keep the volume down during this time also.<sup>15</sup> The same is true for people exposed to ototoxic chemicals in the workplace. Workers exposed to ototoxic chemicals should be advised that it is in their best health interest to keep the volume down on their hearing aids, and to keep the work environment as quiet as is possible.

What is a safe level in such situations? The only thing known for sure is that current standards are not stringent enough. Researchers were surprised to discover that when noise and ototoxic agents team up to damage ears, this damage can occur even though exposure to both noise **and** chemicals are **within currently acceptable limits!**<sup>10</sup>

### **High Frequency Hearing Testing is Important**

Many ototoxic drugs and chemicals begin destroying hearing at the highest frequencies first, and as exposure continues, lower frequencies become involved. Since hearing is traditionally only tested up to 8 kHz, most **initial** cases of hearing loss from ototoxic drugs and chemicals are **never** revealed by standard audiometric testing.

However, high-frequency audiometry is important if hearing loss from ototoxic drugs is to be minimized or prevented. High-frequency audiometry can reveal the early effects of ototoxic drugs before tinnitus appears or hearing damage is visible on a conventional audiogram (250 and 8,000 Hz).

In studies involving **Cisplatin**, the **first** indications of hearing loss **always** appeared between 10,000 and 16,000 Hz.<sup>24</sup> Of course, standard audiometric testing would not have revealed this hearing loss, as it impacts higher than typically tested frequencies.

Several ototoxic chemicals cause **initial** hearing loss in the high frequencies. For example, high-frequency hearing testing revealed that workers exposed to low concentrations of **styrene** fumes for 5 years had hearing losses in the high frequencies even though their hearing tests in the conventional frequencies were normal. If high-frequency hearing testing hadn't been done, **styrene** could have been given a clean bill of health -- even though it is ototoxic.

Inhaling **styrene** fumes is known to cause a reduction in the upper limit of hearing. Researchers concluded that the upper limit of hearing is a sensitive indicator for early detection of ototoxicity in workers exposed to **styrene**<sup>18</sup> and indeed, probably for many or most ototoxic drugs and chemicals.

One study demonstrated that audiometric testing across the conventional hearing range is the **least effective** method to determine initial hearing loss.<sup>5</sup> Therefore, if you want to know whether drugs or chemicals are insidiously stealing your patients' hearing, you

need to test their hearing up to the highest frequency possible.

Since ototoxic hearing loss typically begins at the highest frequencies and progresses through lower ones, audiologists should monitor the highest measurable frequencies in people with pre-existing hearing loss, to provide the earliest possible warning of further drug-related hearing loss.

Early detection does not, by itself, prevent further damage to a person's ears. However, it does give doctors time to adjust the dose or stop the medication altogether before hearing loss spreads to the conventional frequencies.<sup>6</sup> If monitoring is restricted to frequencies below 8000 Hz, by the time audiologists detect new/additional hearing loss, hearing loss will have already affected those frequencies necessary for speech.

How good is high-frequency testing? When researchers compared testing high frequencies versus testing conventional frequencies, one study revealed that 52% of hearing losses were **first** detected in the high-frequency range only. That study revealed that more than half the people with drug-induced hearing loss have hearing loss that was **not** detected by conventional means. If only high-frequency hearing testing had been done, 67% of all the ears demonstrating initial hearing loss due to ototoxicity would have been found.<sup>7</sup>

Another study revealed that only 13.5% of the people (ears) studied had initial drug-related hearing loss in the conventional frequencies. An additional 24% had initial detectable hearing loss in the conventional frequencies as well as the high frequencies. Thus, a whopping 62.5% of drug-induced hearing loss likely goes undetected because it initially **only** occurs in the traditionally not-tested high frequencies!<sup>8</sup> If only the high frequencies had been tested, 86% of all cases of drug-induced hearing loss would have been detected.

Testing all frequencies between 125 Hz and 20,000 Hz is time consuming and of course, adds additional expense to the evaluation. Fortunately, researchers have recently discovered a five-frequency slope that is very sensitive to the ravages of ototoxic drugs. The beauty of this five-frequency slope testing is that it is highly sensitive to **initial** ototoxic hearing loss.

This five-frequency range varies depending on each person's pre-existing hearing loss and thus is unique to each person. These five frequencies are generally separated by 1/6 octave.

For example, a person with pre-existing hearing loss might have a five-frequency slope consisting of 8, 9, 10, 11.2 and 12.5 kHz.<sup>9</sup> Since each person's hearing loss is unique, the testing process is tailored for each person and this can be easily and accurately accomplished.

Using an audiometer calibrated to accurately test up to 20,000 Hz, determine the highest frequency your patient can hear. (Note: the hearing loss at this frequency must be 100 dB

or less.) Second, test this frequency and the next four lower consecutive audiometric test frequencies. This becomes the individual patient's five-frequency slope range.<sup>6</sup>

Depending on the patient's particular hearing loss, this five-frequency slope may all lie within the extended high-frequency range, it may straddle the 8,000 Hz boundary, or it may reside completely within the conventional frequencies.

Just how effective is this five-frequency slope in detecting hearing loss from ototoxic drugs? The results may surprise you!

In one study of the ototoxic effects of **Cisplatin**, if only the five frequencies in the five-frequency slope had been tested, 93% of the people with ototoxic drug-induced hearing loss would have been detected.<sup>6</sup> This is in sharp contrast to the 39% detected in this same study using only the conventional frequencies.

Other studies have yielded similar results. For example, another study reported that if only the five-frequency slope values were tested, hearing loss due to Aminoglycoside antibiotics would be detected 84% of the time, and for **Cisplatin**, the results would be 94%.<sup>9</sup> Another study revealed that initial hearing loss would have been detected in 89% of the people with hearing loss if only the five-frequency slope had been tested. Testing only conventional frequencies caught just 37%.<sup>8</sup>

Based on results such as these, the routine use of high-frequency audiometry is not just "nice," it is essential.<sup>15</sup>

For hospital in-patients who must undergo drug therapy with ototoxic drugs, having complete audiometric testing can be a problem, especially if they are unconscious, semi-conscious or very sick. In such cases, using a conventional audiometer and test protocols is difficult, if not impossible. In these situations, auditory brainstem response (ABR) techniques modified to work in the higher frequencies can be effective tools. In one such study, high-frequency tone-burst-evoked ABRs identified 93% of the initial changes in hearing loss.<sup>7</sup>

The five-frequency slope protocol is fast and efficient and has been proven effective in providing early warning of hearing loss.

I recommend that the five-frequency slope protocol become the accepted standard practice in audiometric testing to help patients save precious hearing that otherwise might be lost to the ravages of ototoxic drugs.

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The information in this paper is taken from the second edition of the book **Ototoxic Drugs Exposed** by the same author. If you would like to learn more about ototoxicity in general, or if you would like to learn the specific ototoxic side effects of the 743 ototoxic drugs, 30 herbs and 148 chemicals mentioned in this book, order your copy of the second edition of **Ototoxic Drugs Exposed** by Neil Bauman from his web site at

<http://www.hearinglosshelp.com/ototoxicdrugbook.htm>.

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