The purpose of this page is to list drugs well known to be toxic to the ear. It is not all-inclusive and it should not be relied upon for medical care.

### CHEMOTHERAPY AGENTS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Vestibulotoxicity</th>
<th>Hearing Toxicity</th>
<th>Toxic Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td></td>
<td>1-10%</td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Minor</td>
<td>69%</td>
<td>total dose &gt;</td>
</tr>
<tr>
<td>nitrogen mustard</td>
<td>yes</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Vincristine</td>
<td>yes</td>
<td>yes</td>
<td></td>
</tr>
</tbody>
</table>

Comment: While reportedly ototoxic, these medications are rarely encountered as a source of vestibular dysfunction. Cisplatin is the most widely used anticancer drug currently and unfortunately, it is cochleotoxic, and may injure supporting cells (Ramirez-Camacho et al, 2004). The toxicity of cisplatin is synergistic with gentamicin, and high doses of cisplatin have been reported to cause total deafness. In animals, cisplatin ototoxicity is related to lipid peroxidation and the use of antioxidant agents such as vitamin E are protective (Rybak et al, 2000; Kalkanis et al, 2004).

There are many chemotherapy agents which have no credible evidence for ototoxicity, and also many in whom there are single case reports of dubious significance. In general, drugs that are "broad" in their effects on the body would be expected to also have some ototoxicity. Drugs that
are very narrow, perhaps aimed at cell markers, would not be reasonably expected to be ototoxic. Some chemotherapy drugs are used in treatment of inner ear disease -- i.e. cytoxin, methotrexate, and Enbrel. These would obviously not be expected to be ototoxic.

Chemotherapy ototoxicity references


ANTIBIOTICS WITH GOOD EVIDENCE FOR OTOTOXICITY

<table>
<thead>
<tr>
<th>Drug</th>
<th>Vestibulotoxicity</th>
<th>Hearing Toxicity</th>
<th>Toxic Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>not toxic</td>
<td>13.9%</td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>not known</td>
<td>occasional</td>
<td>Very high dose required</td>
</tr>
<tr>
<td>Capreomycin</td>
<td></td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td></td>
<td>yes</td>
<td>sporadic reports only</td>
</tr>
<tr>
<td>Dibekacin</td>
<td></td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Dihydrostreptomycin</td>
<td>minor toxic</td>
<td>very toxic</td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td></td>
<td>yes</td>
<td>High IV doses only</td>
</tr>
<tr>
<td>Antibiotic</td>
<td>Toxicity</td>
<td>Ototoxicity</td>
<td>Duration</td>
</tr>
<tr>
<td>----------------</td>
<td>-----------</td>
<td>-------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>8.6%</td>
<td>minor</td>
<td>Usually 2 weeks</td>
</tr>
<tr>
<td>Metronidizole</td>
<td>toxic (rarely)</td>
<td>unknown</td>
<td></td>
</tr>
<tr>
<td>Neomycin</td>
<td>minor</td>
<td>very toxic</td>
<td>In topical ear drops</td>
</tr>
<tr>
<td>Netilmicin</td>
<td>Yes</td>
<td>2.4%</td>
<td></td>
</tr>
<tr>
<td>Polymyxin B</td>
<td></td>
<td></td>
<td>In ear drops</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>very toxic</td>
<td>minor</td>
<td></td>
</tr>
<tr>
<td>Tobramycin</td>
<td>Yes</td>
<td>minor in 6%</td>
<td>Less toxic than Gentamicin</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>nontoxic</td>
<td>none to moderate</td>
<td>synergistic with gentamicin</td>
</tr>
</tbody>
</table>

Comments about antibiotics with well recognized ototoxicity.

Gentamicin is presently the biggest problem antibiotic with respect to ototoxicity as most of the other ototoxic antibiotics have been replaced. Netilmicin has equivalent ototoxicity to Gentamicin (Tange et al, 1995). Gentamicin was released for clinical use in the earlier 1960's. (Matz, 1993); Hearing toxicity generally involves the high frequencies first. Vestibulotoxicity is the major problem rather than hearing toxicity. Most persons with gentamicin toxicity have hearing appropriate for their age. Certain persons with mitochondrial deletions in the 12S subunit are much more susceptible to Gentamicin than the general population. Commercial tests are presently available to detect this deletion (the A1555 deletion). The prevalence of this mutation is not clear, but 1-2% of the population is estimated based on available data. It is likely that there are many other genetic mutations that confer susceptibility, so far undocumented by present day medicine.

Neomycin, another aminoglycoside, was isolated in 1949. It is now used mainly topically because of renal toxicity and ototoxicity (to hearing). Neomycin is poorly absorbed from the normal gastrointestinal tract -- about 97% is excreted in the feces. Neomycin is quickly and almost totally absorbed from body surfaces (except the urinary bladder) after local irrigation and when applied topically in association with surgical procedures. With repeated dosing, progressive accumulation occurs in the inner ear. Release occurs slowly over several weeks after dosing has been stopped. Hearing ototoxicity from oral absorption of Neomycin has been reported (Rappaport et al, 1986) and there may also be toxicity from ear drops in patients with perforated ear drums. This issue is still unsettled (as of 12/1/98). Neomycin toxicity is often delayed in onset and may not be noted until long after neomycin has been discontinued (Information primarily from the manufacturers literature, Teva Pharmaceuticals, 11/1999).
Kanamycin, also an aminoglycoside, was developed in 1957, and has been replaced by newer aminoglycosides such as gentamicin, tobramycin, netilmicin, and amikacin. It is not thought to be as ototoxic as neomycin.

Streptomycin, the first clinically used aminoglycoside is now used primarily in treating tuberculosis because many gram-negative bacteria are resistant and because of substantial ototoxicity. Streptomycin is now rarely used in the United States.

Tobramycin is only rarely associated with ototoxicity (about 1/150 according to Neu et al, 1986), but there is clear evidence that it can produce a vestibular syndrome similar to gentamicin (Barrsma, 1979; Lehmann, 1976). Most cases of Tobramycin toxicity have occurred in persons with renal impairment. There has been little ototoxicity seen in persons with repeated dosing (Pedersen et al, 1987; Thomesen et al, 1979), which suggests that it may be handled differently by the ear. It is suspected that tobramycin is ototoxic to hearing in neonates but there is little evidence to prove this (de Hoog et al, 2002; 2003). In animals, tobramycin is much less ototoxic than gentamicin (Bamonte et al, 1986; Kitasato, 1990; McCormick et al, 1985; Petorossi et al, 1986).

Vancomycin, by itself, appears to have only minor ototoxicity, but it potentiates the ototoxicity of gentamicin as well as (probably) other aminoglycosides such as Tobramycin. Occasional persons do appear to have substantial vestibular toxicity from Vancomycin. The reason why occasional persons are more sensitive is not clear but might resemble the situation with Gentamicin where there is a susceptibility mutation.

**References concerning specific antibiotics:**

Related to tobramycin

Antibiotics for which there is some suspicion of ototoxicity

<table>
<thead>
<tr>
<th>Antibiotic with suspected ototoxicity</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Floxins</td>
<td>Anecdotal evidence of dizziness</td>
</tr>
</tbody>
</table>

Comment: Although there is some evidence for dizziness, it is unlikely that the floxins are ototoxic.

Occasionally a persistent ataxia is reported following use of a floxin (e.g. ciprofloxacin, etc). All cases so far are anecdotal and there is no strong evidence for ototoxicity. Toxicity, if it exists, might involve some other structure (such as the cerebellum). Because toxicity is so sporadic it may require both exposure as well as a genetic predisposition for toxicity.

Also, some of the floxins can have an affect on blood glucose. Gatifloxicin (Tequin) can cause severe persistent hypoglycemia in elderly diabetics taking hypoglycemic drugs, and may cause hyperglycemia in patients with no history of diabetes (Medical letter, 2003). While these effects are not ototoxic, they might account for some dizziness side effects, which should respond to withdrawal of medication.

Antibiotics generally considered safe
Macrolides and other antibiotics that are only slightly ototoxic:

Azithromycin, is a macrolide -- and not in the same family as Gentamicin. Nevertheless, there are occasional reports of ototoxicity, when there have been prolonged and high levels. The high levels generally require intravenous dosing.

Clindamycin has not been reported to cause ototoxicity, by itself, and is probably safe.

Chloramphenicol has been sporadically reported to be ototoxic systemically.

Erythromycin, although not an aminoglycoside like gentamicin, is ototoxic in high intravenous doses. (McGhan et al. 2003) Pathologically McGhan and Merchant reported strial edema in all of the cochlear turns (in a single case report). This might account for the relatively flat threshold loss with good speech discrimination that is the hallmark of erythromycin ototoxicity. It might also account for some reversibility to the hearing loss.

Metronidizole (Flagyl) has been reported on several occasions to be ototoxic (Blake and Butt 1984; Hibberd, Nicoll et al. 1984; Hibberd, Nicoll et al. 1984; Lawford and Sorrell 1994; Iqbal, Murthy et al. 1999; Riggs et al, 1990). Metronidazole toxicity fortunately appears to be rare and documented only by sporadic case reports.

References r.e. Metronidizole:


References re macrolides:
**Other useful information about ototoxins**

**Ear drops** may contain antibiotics, some of which can be ototoxic when administered to persons with perforated ear drums. Cortisporin otic solution appears to be the most ototoxic to the cochlea of guinea pigs, with much less toxicity for gentamicin drops. Ofloxacin ear drops have negligible toxicity (Barlow et al, 1995). Neomycin containing ear drops have been reported to contribute to hearing loss (Podoshin et al, 1989) in a relatively small way, but a definitive assessment of risk has not yet been made. No cases have been reported of tobramycin drops resulting in ototoxicity. The vestibulotoxicity of most ear drops has so far not been studied, although case reports suggest that gentamicin containing drops are toxic when given over long periods of time.

There are several known *interactions* between families of ototoxic medications. Loop diuretics (see following) potentiate aminoglycoside toxicity. Vancomycin is synergistic with gentamicin in that it is more likely to cause toxicity, as is noise. Vancomycin, by itself in appropriate doses, is not ototoxic (Gendeh et al, 1998).

*Delayed ototoxicity*, meaning essentially toxicity which continues for several months after the drug has been stopped, has been well documented because the aminoglycosides are retained within the inner ear much longer than in the blood. Gentamicin has been reported to persist for more than 6 months in animals. Neomycin, streptomycin and kanamycin are also known to be eliminated from the inner ear slowly (Thomas et al, 1992)

**References regarding ototoxicity of antibiotics:**

- Bates RD, Nahata MC, Jones JW, McCoy K, Yong G, Cox S, Barson WJ. Pharmacokinetics and safety of tobramycin after once-daily administration in patients
with cystic fibrosis. Chest 112(5):1208-13, 1997. This paper notes no ototoxicity in 18 patients for once/day administration.

- Riggs LC, Shofner WP, Shah AR, Young MR, Hain TC, Matz GJ. Ototoxicity resulting from combined administration of metronidazazole and gentamicin. Am J Otol 20, 4, 1990, 430-
- Vasquez R, Mattucci K. A proposed protocol for monitoring ototoxicity in patients who take cochleo- or vestibulotoxic drugs. ENT J. 82:3, 181-184

**OTOTOXIC DIURETICS**
Diuretics generally considered Safe: Chlorthiazide

Diuretics are rarely a source of vestibulotoxicity. They are possibly a source of hearing disturbance. They may be synergistic with other aminoglycoside ototoxins such as gentamicin, neomycin, streptomycin and kanamycin. It seems prudent to attempt to avoid exposure to these agents if hearing is impaired.


**QUININE DERIVATIVES**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Vestibulotoxicity</th>
<th>Hearing Toxicity</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinidex</td>
<td>No</td>
<td>Yes</td>
<td>Tinnitus</td>
</tr>
<tr>
<td>Atabrine</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Plaquenil</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Quinine Sulfate</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>mefloquine (Lariam)</td>
<td>Probable</td>
<td>Yes</td>
<td>Tinnitus and dizziness</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Unlikely</td>
<td>Rare</td>
<td>Hearing loss</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>No reports</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>
Comment: While quinine ingestion can cause a syndrome including tinnitus, sensorineural hearing loss and vertigo, quinine derivative drugs are rarely by themselves a source of hearing disturbance. Some quinine derivatives, such as mefloquine (Larium) taken for malaria prevention rarely cause significant and long-lasting tinnitus. There is also some suspicion of vestibulotoxicity and CNS toxicity (Dow et al, 2006). Recent studies suggest that quinine impairs outer hair cell motility (Jarboe and Hallworth, ARO abstracts, 1999, #237).

References:


We thank Lariam Action USA (email LariamInfo@yahoo.com; web site http://www.lariaminfo.org/), for supplying some of the references above related to lariam.

ASPIRIN, NSAIDS and other ANALGESICS

Aspirin and Nsaids (non-steroidal anti-inflammatory agents) -- commonly used, and apparently only toxic to hearing. These include Advil, Nuprin, Motrin (Ibuprofen), Aleve, Naprosyn, Anaprox (Naproxen), Feldene, Dolobid, Indocin, Lodine, Relafin, Toradol, Volteran, Salicylates: Aspirin, disalcid, Bufferin, Ecotrin, Trilisate, Ascriptin, Empirin, Excedrin, Fiorinal. Arthrotec (diclofenac and misoprostel) has been associated with tinnitus and hearing reduction (Bombardier, Peloso et al. 1995).

Hydrocodone in combination with acetaminophen (e.g Vicodin) has also been associated with hearing loss (Friedman, House et al. 2000; Oh, Ishiyama et al. 2000). Complete deafness, treated with a cochlear implant, can occur in persons addicted to these medications. This clinical picture is sometimes misdiagnosed as autoimmune inner ear disease.

Fiorinal contains aspirin, which is well known to be an ototoxin capable of causing a sensorineural hearing loss and tinnitus (Brien 1993).
Over the counter headache powders also commonly contain aspirin or related compounds (salicylates) and therefore have a potential for causing hearing toxicity.

Permanent hearing disturbances are possible but rare. They are most commonly seen in individuals who take aspirin in large doses for long periods, such as for treatment of severe arthritis. Occasionally persons with Menieres syndrome will develop a hearing disturbance from a small amount of a NSAID.

Acetaminophen is not generally thought to be ototoxic although in combination with hydrocodone as noted above there have been cases of hearing loss.

**Organic solvents:**

Styrene, Toluene, and trichloroethylene have been reported to be ototoxic. These substances are highly lipid soluable and can also be neurotoxic. Their toxicity may be due to effects on central structures rather than the ear itself.

**References:**

- Oh AK, Ishiyama A, Baloh R. Deafness associated with abuse of hydrocodone/acetaminophen.Naproxen has been associated with deafness (Kewitz 1986; McKinnon and Lassen 1998). I have also encountered patients reporting tinnitus and hearing reductions after taking Naproxen.

**Other drugs**

Although nearly all antidepressants impair balance, the mechanism of this effect is uncertain, and probably not due to ototoxicity.

A single case has been reported of deafness following ingestion of sildenafil. This involved a 44 year old man who took 50 mg every day for 15 days (Mukherjee and Shivakumar, 2006).

## MISCELLANEOUS OTOTOXIC DRUGS

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Vestibulotoxicity</th>
<th>Hearing Toxicity</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>PTU</em></td>
<td><em>No</em></td>
<td><em>Yes</em></td>
<td></td>
</tr>
<tr>
<td><em>Desferroxamine</em></td>
<td><em>No</em></td>
<td><em>Yes</em></td>
<td>May protect against gentamicin toxicity</td>
</tr>
<tr>
<td>hexadimethrine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Polybrene)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium Channel</td>
<td>Probably</td>
<td>No evidence of this to date</td>
<td></td>
</tr>
<tr>
<td>blockers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Sulfonamides</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Phenylbutazine</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</td>
<td></td>
<td><em>Yes</em></td>
<td>Weak evidence (see Rifal, 2006)</td>
</tr>
</tbody>
</table>

Calcium channel blockers are often used to treat vestibular disorders, and by this reasoning, might be vestibular suppressants. In the authors practice, rarely calcium channel blockers appear to be associated with bilateral vestibular paresis, but nothing has written about this in the literature.

### References:


### Other Toxins (not medications):
• Carbon monoxide: There is a small literature, nearly all published in languages other than English, concerning cochlear and vestibulotoxicity from carbon monoxide (CO) poisoning. To us, it seems highly unlikely that CO would injure the vestibular apparatus in a selective fashion, and we consider CO induced isolated vestibular toxicity as highly unlikely.

• Mercury and lead are heavy metals which are ototoxic. Practically speaking, these agents are infrequent causes of hearing disturbance.

• Toluene affects the ear (outer hair cells) causing hearing loss, as well as the brain.

• Noise: e.g. Rock concerts, power equipment, gunfire.
  - Noise exposure is the most common source of hearing loss. Industrial exposure characteristically causes a "noise notch", with the hearing loss at mid-high frequencies bilaterally. Guns and other unilateral sources of noise cause more circumscribed lesions. Noise is often also a co-factor in medication type ototoxicity. Those who have hearing loss from an ototoxic antibiotic, for example, may be at much greater risk from noise. There is some evidence that heavy salt eaters are more susceptible to damage from noise.

**Protection from ototoxins**

Little is known about protection. Noise avoidance is likely important, but even here the story is complicated. Moderate amounts of noise may protect from extreme amounts of noise. Antioxidants protect partially from noise or toxins in several animal models. In theory, protection from oxidative stress might be obtained by prevention of reactive oxygen species, neutralization of toxic products, and blockage of the apoptosis pathway. Toxic waste products can be neutralized with glutathione and derivatives (Rybak et al, 2000). Vitamin E may protect against cisplatin ototoxicity (Kalkanis, Whitworth et al. 2004). Apoptosis can be blocked using capsase inhibitors. At this writing, 2/1999, all of these approaches are investigational and are not being used clinically. Most also require delivery systems that go directly into the inner ear, and are therefore impractical for clinical use (Van de Water and others, ARO abstracts, 1999, #21).

References:


**General references:**