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## **Evidence-Based Systematic Review (EBSR): Drug-Induced Hearing Loss— Aminoglycosides**

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### **Introduction**

*Ototoxicity* refers to a toxic or poisonous reaction causing damage to the inner ear, the auditory system, and/or the vestibular system (American Speech-Language-Hearing Association [ASHA], 1994; Handelsman, 2007). Often drug induced, this toxic reaction can lead to hearing loss for many individuals. The hearing loss can manifest in one or both ears, range from a mild to a severe impairment, and have temporary or long-lasting effects. Regardless of the type or severity, drug-induced hearing loss can have devastating effects on communication and can lead to difficulties in educational, vocational, and social settings for both children and adults (ASHA, 1994).

An ototoxic effect within the class of aminoglycoside drugs was first documented with streptomycin (Hinshaw & Feldman, 1945). Introduced in 1940, streptomycin was used to treat tuberculosis (Kingston, 2004). With the success of this drug, the development of other aminoglycosides such as neomycin, kanamycin, gentamicin, amikacin, tobramycin, and netilmicin soon followed. Today, aminoglycoside treatments are commonly used to fight against gram-negative bacteria or mycobacteria to treat

septicemia, respiratory infections, urinary tract infections, skin infections, and tuberculosis, despite the ototoxic effects being well established in a number of published systematic reviews and meta-analyses (Ali & Goetz, 1997; Blaser & Konig, 1995; Contopoulos-Ioannidis, Giotis, Baliatsa, & Ioannidis, 2004; Galloe, Graudal, Christensen, & Kampmann, 1995; Hatala, Dinh, & Cook, 1996; Kale-Pradhan, Habowski, Chase, & Castronova, 1998; Munckhof, Grayson, & Turnidge, 1996; Nestaas, Bangstad, Sandvik, & Wathne, 2005; Smyth & Bhatt, 2006). Although many reviews detail the ototoxic effects of these drugs, the incidence of hearing loss resulting from aminoglycoside treatment remains disputed (Brummett & Fox, 1989).

Data reported on the incidence of hearing loss after aminoglycoside treatment range from 0% (Powell, Thompson, & Luthe, 1983) to 63% (Tablan, Reyes, Rintelmann, & Lerner, 1984). This wide variability in incidence may be attributable to a number of factors such as age (Axdorph, Laurell, & Bjorkholm, 1993), previous or concomitant exposure to other ototoxic medications (Maller, Ahrne, Eilard, Eriksson, & Lausen, 1991), or genetic predisposition (Gurtler et al., 2005). Differences in drug administration, such as dosing, schedule/timing, route of administration (e.g., intravenous vs. intramuscular), or drug combinations (de Jager & van Altena, 2002; de Vries, Verkooyen, Leguit, & Verbrugh, 1990; Ibrahim et al., 1990) also further compound this issue.

Other factors contributing to this discrepancy include the evaluation of hearing and the definition of ototoxicity reported across studies. Aminoglycosides have been known to affect hearing exclusively or initially in higher frequencies (9–20 kHz) prior to presentation of hearing loss in lower frequencies (Dreschler, van der Hulst, Tange, & Urbanus, 1985; Fausti et al., 1992). Therefore, studies that report hearing loss on the basis of patient complaint or testing across the conventional frequency range (250–8000 Hz) may underestimate the ototoxic effects of these drugs. Additionally, these drugs accumulate in the inner ear fluid and are slowly eliminated. This can result in a delay or progression in hearing loss once treatment has ended, such that any later-identified hearing loss may be inaccurately disregarded as unassociated with the drug treatment (Myerhoff, Malle, Yellin, & Roland, 1989).

Conversely, many standard audiometric definitions of ototoxicity may inflate the incidence of drug-induced hearing loss. A study by Brummett and Morrison (1990) investigated a definition of ototoxicity often used in studies (a  $\geq 15$ -dB increase in pure-tone threshold at two or more frequencies or a  $\geq 20$ -dB increase at one frequency) and found a 20%–33% incidence rate of hearing loss among 20 healthy participants without ototoxic drug exposure. The authors concluded that estimates of ototoxicity may be exaggerated and that many of these reported threshold changes likely reflect normal test–retest variability from serial audiometric testing.

Although the incidence of aminoglycoside-induced hearing loss is a complex issue, audiologists involved in the diagnosis and management of individuals with hearing loss should be aware of the scientific evidence pertaining to these toxic medications. Understanding the effects of aminoglycoside treatments and their impact on hearing can assist clinicians with early detection and audiological management.

As such, ASHA's National Center for Evidence-Based Practice in Communication Disorders (N-CEP) conducted a series of evidence-based systematic reviews (EBSRs) investigating the effects of aminoglycoside treatment on hearing. This report details the methodology used to conduct the series of EBSRs targeting aminoglycoside treatments. The document outlines the clinical questions addressed across the series of reviews; the search parameters, including inclusion/exclusion criteria; the process used to critically appraise the included studies; and the literature search results. Subsequent reports will present the individual findings for each targeted aminoglycoside drug.

## **Method**

### *Development of Clinical Questions*

When formulating the clinical questions for review, a number of parameters were considered. These included the short- and long-term effects of aminoglycoside treatments on hearing (Clinical Questions 1 and 2), various characteristics related to treatment delivery (Clinical Questions 3–5), and the synergistic effect on hearing with concomitant treatment of other potentially ototoxic medications (Clinical Question 6). Initially, 11 drugs within the aminoglycoside family were targeted in each clinical question; these drugs included amikacin, dibekacin, gentamicin, isepamicin, kanamycin, neomycin, netilmicin, paromomycin, sisomicin, streptomycin, and tobramycin. The following six clinical questions were identified for review.

1. What is the likelihood of persons treated with target aminoglycoside developing hearing loss?
2. What is the persistence of hearing loss in persons treated with target aminoglycoside?
3. Is the likelihood of aminoglycoside-induced hearing loss affected by dosage?
4. Is the likelihood of aminoglycoside-induced hearing loss affected by route of administration?
5. Is the likelihood of aminoglycoside-induced hearing loss affected by schedule of administration?
6. Is there evidence of a synergistic effect on hearing loss if multiple ototoxic drugs (i.e., aminoglycosides, antineoplastics) are taken concomitantly with target aminoglycoside?

Each question was broken down by target aminoglycoside (amikacin, dibekacin, gentamicin, isepamicin, kanamycin, neomycin, netilmicin, paromomycin, sisomicin, streptomycin, and tobramycin).

### *Literature Search*

A literature search was completed from February 2009 to March 2009 on the broader topic of drug-induced vestibulotoxicity and cochleotoxicity from several classes of drugs, including aminoglycosides, antineoplastics, and loop diuretics. Table 1 outlines the electronic databases searched pertaining to this series of EBSRs on aminoglycosides. A manual search of relevant authors and journals was also completed along with a search for guidelines from various organizational Web sites. The list of Web sites, along with the full search string, is provided in Appendix A.

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**Table 1.** Electronic databases searched for systematic review series.

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- Centre for Reviews and Dissemination
  - Cumulative Index to Nursing and Allied Health Literature (CINAHL)
  - Cochrane Library
  - ComDisDome
  - Communication & Mass Media Complete
  - Health Source: Nursing/Academic Edition
  - Linguistics and Language Behavior Abstracts
  - National Guideline Clearinghouse
  - PubMed
  - Science Citation Index
  - Social Science Citation Index
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### *Inclusion/Exclusion Criteria*

Studies were considered for the review if they were published in a peer-reviewed journal from January 1990 to March 2009, were written in English, and reported original data on human subjects targeting one or more of the six clinical questions outlined above. Studies were excluded if the type of aminoglycoside drug was not specified, if treated individuals had a diagnosis of Meniere's disease, or if a case study design was used. Additionally, studies were excluded if data for individual aminoglycoside drugs were not analyzed separately or if a definition of hearing loss was not reported. An exception to this was the inclusion of controlled trials in which comparative findings on dosage, schedule, or route of drug administration were reported.

Following the search, it was noted that five of the target drugs (isepamicin, netilmicin, dibekacin, paromomycin, and sisomicin) were not available for use in the United States; therefore, studies examining the effects of these drugs were also excluded. Additionally, three target drugs—neomycin, kanamycin and streptomycin—did not have sufficient, current evidence bases for conducting meaningful systematic reviews. The remaining aminoglycosides (gentamicin, tobramycin, and amikacin) are addressed separately in three systematic reviews.

### *Critical Appraisal of the Evidence*

Accepted studies were then appraised for methodological quality and summarized based on participant/intervention characteristics and major findings. Each study was evaluated by two reviewers blind to one another's results on the following six criteria.

1. Was the sample of patients clearly defined (diagnoses reported)?
2. Was pre-hearing status reported for all patients?
3. Was follow up completed on > 80% of patients (post-treatment hearing assessment)?
4. Were outcome measures objective and clearly defined?
5. Were assessors blinded to intervention (i.e., drug, dosage, route of administration)?
6. Did all patients receive the same treatment regime/dosage? If not, were data adjusted by regime/dosage?

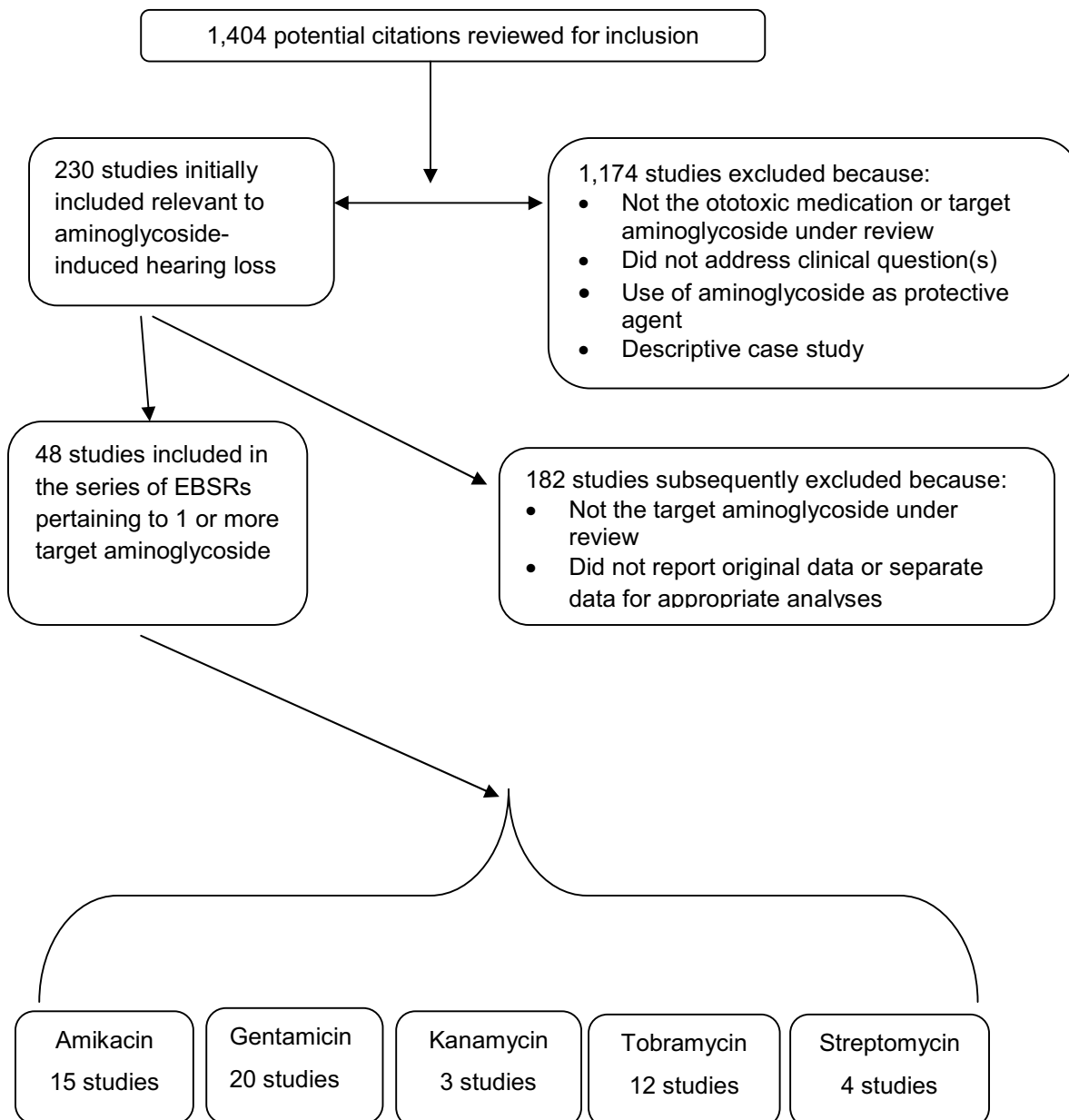
A quality score was tallied for each study. Studies received 1 point for each area that met the above criteria, with a maximum score of 6. Agreement among independent reviewers was tracked and was found to be 90%. Any discrepancies in inclusion/exclusion or quality ratings were resolved via consensus. A final synthesis of the evidence was broken down by specific aminoglycoside intervention and the corresponding clinical question(s). The results and corresponding discussion sections are included in separate EBSR reports for each of the targeted aminoglycosides.

## **Results**

Three reviewers independently assessed 1,404 abstracts (see Figure 1) and initially identified 230 citations as meeting the inclusion criteria. Of these, 179 were subsequently excluded because they examined the effects of drugs other than the six

target aminoglycosides (e.g., loop diuretics, carboplatin, cisplatin, isepamicin, etc.) or because the original data were not reported or could not be analyzed. A total of 48 studies reported hearing outcomes associated with the administration of one or more of the target aminoglycosides and were included in this series of EBSRs. Reliability among reviewers for inclusion into the review series was 85%.

**Figure 1.** Process for inclusion of studies.



Of the 48 included studies, 20 examined the effects of gentamicin, 15 examined the effects of amikacin, 12 examined the effects of tobramycin, four examined the effects of streptomycin, and three targeted the use of kanamycin. No studies examining the effects of neomycin met the inclusion criteria for these reviews. This total exceeds 50, as several studies were found to address multiple drugs targeted in this series of EBSRs (see Table 2).

**Table 2.** Studies included in the series of systematic reviews.

Study	Amikacin	Gentamicin	Tobramycin	Streptomycin	Kanamycin
Agarwal et al. (2002)		X			
Axdorph et al. (1993)	X				
Bailey et al. (1996)		X			
Bates et al. (1997)			X		
Blum (1995)	X				
The International Antimicrobial Therapy Cooperative Group <sup>a</sup> (1993)	X				
Charnas et al. (1997)	X				
Chayasirisobhon et al. (1996)		X			
Cheung et al. (1990)		X			
Chong et al. (2003)		X			
de Hoog et al. (2003)			X		
de Hoog et al. (2002)			X		
de Jager & van Altena (2002)	X			X	X
El Bakri et al. (2000)		X			
Elhanan et al. (1995)		X			
Fausti et al. (1999)	X	X	X		
Forsyth et al. (1997)	X				

(continued)

**Table 2** (continued)

Study	Amikacin	Gentamicin	Tobramycin	Streptomycin	Kanamycin
Gendeh et al. (1993)		X			
Gendeh et al. (1991)		X			
Giamarellou et al. (1991)	X				
Gorse et al. (1992)			X		
Haydon et al. (1993)		X			
Ibrahim et al. (1990)	X				
Indudharan et al. (2005)		X			
Kafetzis et al. (2000)	X				
Kharkheli et al. (2007)		X			
Kos et al. (2003)		X			
Kotze et al. (1999)	X				
Langhendries et al. (1993)	X				
Li et al. (1991)			X		
Lima et al. (2006)				X	
Maller et al. (1991)	X				
Mukhopadhyay et al. (1993)			X		
Nikolaidis et al. (1991)			X		
Nordström et al. (1990)		X			
Peloquin et al. (2004)	X			X	X
Prins et al. (1994)		X			
Ramsey et al. (1993)			X		
Ramsey et al. (1999)			X		
Raz et al. (1995)		X			

(continued)



**Table 2** (continued)

Study	Amikacin	Gentamicin	Tobramycin	Streptomycin	Kanamycin
Rodriguez-Noriega et al. (1995)	X				
Sánchez-Alcaraz et al. (1998)			X		
Singhal et al. (1992)		X			
Smyth et al. (2005)			X		
Stavroulaki et al. (2002)		X			
Viscoli et al. (1991)	X				
Voogt & Schoeman (1996)				X	X
Whatley et al. (2006)		X			

<sup>a</sup>The full spellout of this group's name is The International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer.

## Discussion

A systematic review of the scientific literature was conducted to examine the state of the evidence regarding hearing loss and aminoglycoside treatments. A series of EBSRs was completed to address the effects of six aminoglycoside treatments on incidence of hearing loss. Six clinical questions were identified for review to address the long- and short-term effects of aminoglycoside treatment on hearing loss incidence as well as the influence of aminoglycoside delivery schedules. A total of 48 studies were identified as meeting predetermined inclusion/exclusion criteria across the series of reviews. The findings from three aminoglycoside treatments are reported in the companion EBSR reports. These reports are intended to help audiologists who are engaging in evidence-based clinical decision making. Additionally, the findings may be used by audiologists to inform physicians and patients of potential adverse toxic effects of specific aminoglycoside treatments and may lead to modifications in aminoglycoside treatment delivery.

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\*Indicates studies included in this EBSR series

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## **Appendix A.** List of organization web sites.

*The literature search was conducted from February 2009 to March 2009. References were managed using the bibliographic software EndNote. The reference lists of all relevant articles identified were scanned for other possible studies. The following organization Web sites were also searched for relevant guidelines:*

American Academy of Neurology  
American Academy of Otolaryngology–Head and Neck Surgery  
American Association for the Deaf-Blind  
American Auditory Society  
American Cancer Society  
American Hearing Research Foundation  
American Neurotology Society  
American Otological Society  
American Speech-Language-Hearing Association  
Association for Research in Otolaryngology  
Association of Academic Physiatrists  
Association of Late-Deafened Adults  
Audiology Australia  
BEGINNINGS for Parents of Children Who Are Deaf or Hard of Hearing  
Better Hearing Institute  
British Association of Otolaryngologists–Head and Neck Surgeons  
British Society of Audiology  
Brazilian Academy of Audiology  
Canadian Association of Speech-Language Pathologists and Audiologists  
Canadian Academy of Audiology  
Colombia Association of Audiology  
Deafness Research Foundation  
Department of Veterans Affairs  
Directors of speech and hearing programs in state health and welfare agencies  
Dutch Audiological Society  
EAR Foundation  
Educational Audiology Association  
European Federation of Audiology Societies  
German Audiology Society  
Health Canada  
Hearing International  
Hong Kong Society of Audiology  
House Ear Institute  
International Bureau for Audiophonology  
International Collegium of Rehabilitative Audiology  
Iranian Audiology Association  
Israeli Speech and Hearing Association  
Italian Society of Audiology  
Joint Committee on Infant Hearing  
Military Audiology Association

National Association of the Deaf  
National Center for Rehabilitative Audiology Research  
National Center on Deafness  
National Hearing Conservation Association  
National Institute on Clinical Excellence  
New York Department of Health  
New Zealand Audiological Society  
New Zealand Guidelines Group  
Ontario Medical Association  
Pan American Society of Audiology  
Philippine Society of Audiology  
Russian Audiological Society  
Scottish Intercollegiate Guidelines Network  
Society for Ear, Nose and Throat Advances in Children  
Society of Otorhinolaryngology and Head-Neck Nurses  
South African Association of Audiologists  
The Trilogical Society  
Vestibular Disorders Association  
World Federation of the Deaf

## Search Terms:

"Antineoplastic Agents"[Mesh] OR "Cisplatin"[Mesh] OR "Carboplatin"[Mesh] OR "Vinca Alkaloids"[Mesh] OR "Vinblastine"[Mesh] OR "Vincristine"[Mesh] OR "vinorelbine "[Substance Name] OR "Eflornithine"[Mesh] OR "Dactinomycin"[Mesh] OR "Bleomycin"[Mesh] OR "Nitrogen Mustard Compounds"[Mesh] OR "Methotrexate"[Mesh] OR "Aminoglycosides"[Mesh] OR "Gentamicins"[Mesh] OR "Gentamicins"[Mesh] OR "Neomycin"[Mesh] OR "Streptomycin"[Mesh] OR "Tobramycin"[Mesh] OR "Sisomicin"[Mesh] OR "Paromomycin"[Mesh] OR "Amikacin"[Mesh] OR "Dibekacin"[Mesh] OR "isepamicin "[Substance Name] OR "Netilmicin"[Mesh] OR "Erythromycin"[Mesh] OR "Vancomycin"[Mesh] OR "Chloramphenicol"[Mesh] OR "Furazolidone"[Mesh] OR "Polymyxins"[Mesh] OR "Trimethoprim-Sulfamethoxazole Combination"[Mesh] OR "Sodium Potassium Chloride Symporter Inhibitors"[Mesh] OR "Furosemide"[Mesh] OR "Bumetanide"[Mesh] OR "Quinine"[Mesh] OR "Ethacrynic Acid"[Mesh] AND "Ear Diseases"[MeSH]

Chemoth\* AND ("Ear Diseases"[MeSH])

("Hearing Tests"[Mesh] OR "Vestibular Function Tests"[Mesh] OR Vestibule, Labyrinth"[Mesh] OR "Hearing"[Mesh]) AND ("Antineoplastic Agents"[Mesh] OR "Cisplatin"[Mesh] OR "Carboplatin"[Mesh] OR "Vinca Alkaloids"[Mesh] OR "Vinblastine"[Mesh] OR "Vincristine"[Mesh] OR "vinorelbine "[Substance Name] OR "Eflornithine"[Mesh] OR "Dactinomycin"[Mesh] OR "Bleomycin"[Mesh] OR "Nitrogen Mustard Compounds"[Mesh] OR "Methotrexate"[Mesh] OR "Aminoglycosides"[Mesh] OR "Gentamicins"[Mesh] OR "Gentamicins"[Mesh] OR "Neomycin"[Mesh] OR "Streptomycin"[Mesh] OR "Tobramycin"[Mesh] OR "Sisomicin"[Mesh] OR "Paromomycin"[Mesh] OR "Amikacin"[Mesh] OR "Dibekacin"[Mesh] OR "isepamicin "[Substance Name] OR "Netilmicin"[Mesh] OR "Erythromycin"[Mesh] OR "Vancomycin"[Mesh] OR "Chloramphenicol"[Mesh] OR "Furazolidone"[Mesh] OR "Polymyxins"[Mesh] OR "Trimethoprim-Sulfamethoxazole Combination"[Mesh] OR "Sodium Potassium Chloride Symporter Inhibitors"[Mesh] OR "Furosemide"[Mesh] OR "Bumetanide"[Mesh] OR "Quinine"[Mesh] OR "Ethacrynic Acid"[Mesh] OR chemoth\*) AND ("1990"[Publication Date] : "2009"[Publication Date])

DE="drug effects"

KW=(antineoplastic OR aminoglycoside OR chemotherapy OR chemotherapeutic OR loop OR vinca OR amikacin OR bleomycin OR bumetanide OR carboplatin OR chloramphenicol OR cisplatin OR dactinomycin OR dibekacin OR difluoromethylornithine OR erythromycin OR ethacrynic OR furzolidone OR ferosemide OR gentamicin OR isepamicin OR kanamycin OR methotrexate OR netilmicin OR nitrogen OR mustard OR paramycin OR polymysin OR quinine OR sisomicin OR

streptomycin OR tobramycin OR trimethoprim-sulfamethoxazole OR vancomycin OR  
vinblastine OR vincristine OR vinorelbine)

("vestibular disorders" OR "hearing disorders") AND ("drug interactions" OR "drug  
toxicity")

("drug interactions" or "drug toxicity") and ("hearing disorders" or "vestibular disorders"  
or "vertigo" or "intralabyrinthine cochleovestibular disorders" or "meniere s disease" or  
"endolymphatic hydrops" or "cochlear meniere s disease" or "vestibular meniere s  
disease" or "Iermoyez syndrome" or "labyrinthitis" or "labyrinthine fistula" or "otosclerosis"  
or "trauma" or "viral infection" or "polio" or "polio as an etiology of flaccid dysarthria" or  
"meningitis" or "meningitis as an etiology of flaccid dysarthria" or "syphilis" or "tumors"  
or "hereditary syndromes" or "acquired syndromes" or "motion sickness" or "congenital  
vestibular asymmetry" or "benign paroxysmal positional vertigo bppv" or  
"extralabyrinthine cochleovestibular disorders" or "intracanalicular tumor" or  
"cerebellopontine angle tumor" or "anomalous blood vessel" or "herpes zoster oticus" or  
"toxic vestibular neuronitis" or "viral neuronitis" or "drop attack" or "presbyvertigo" or  
"disequilibrium" or "nystagmus" or "aetropic nystagmus" or "caloric nystagmus" or  
"down beating nystagmus" or "gaze nystagmus" or "geotropic nystagmus" or "jerk  
nystagmus" or "left beating nystagmus" or "optokinetic nystagmus okn" or "positional  
nystagmus" or "positional alcoholic nystagmus pan" or "right beating nystagmus" or  
"rotary nystagmus" or "up beating nystagmus" or "benign paroxysmal positional  
nystagmus bppn")

("amikacin" or "aminoglycosides" or "amikacin" or "dihydrostreptomycin" or "garamycin"  
or "gentamicin" or "kanamycin" or "neomycin" or "netilmicin" or "streptomycin" or  
"tobramycin" or "viomycin" or "aminoglycosides as a class of ototoxic drugs" or  
"amikacin" or "dihydrostreptomycin" or "garamycin" or "gentamicin" or "kanamycin" or  
"neomycin" or "netilmicin" or "streptomycin" or "tobramycin" or "viomycin" or  
"antineoplastics" or "carboplatin" or "cisplatin" or "carboplatin" or "cisplatin" or  
"cochleotoxic drugs" or "gentamicin" or "kanamycin" or "loop diuretics" or "neomycin" or  
"netilmicin" or "ototoxic drugs" or "aminoglycosides" or "amikacin" or  
"dihydrostreptomycin" or "garamycin" or "gentamicin" or "kanamycin" or "neomycin" or  
"netilmicin" or "streptomycin" or "tobramycin" or "viomycin" or "aminoglycosides as a  
class of ototoxic drugs" or "cochleotoxic drugs" or "vestibulotoxic drugs" or  
"antineoplastics" or "carboplatin" or "cisplatin" or "antimitotics" or "antimalarials" or  
"salicylates" or "loop diuretics" or "quinine" or "streptomycin" or "tobramycin" or  
"vestibulotoxic drugs")

((("amikacin" or "aminoglycosides" or "amikacin" or "dihydrostreptomycin" or "garamycin"  
or "gentamicin" or "kanamycin" or "neomycin" or "netilmicin" or "streptomycin" or  
"tobramycin" or "viomycin" or "aminoglycosides as a class of ototoxic drugs" or

"amikacin" or "dihydrostreptomycin" or "garamycin" or "gentamicin" or "kanamycin" or "neomycin" or "netilmicin" or "streptomycin" or "tobramycin" or "viomycin" or "antineoplastics" or "carboplatin" or "cisplatin" or "carboplatin" or "cisplatin" or "cochleotoxic drugs" or "gentamicin" or "kanamycin" or "loop diuretics" or "neomycin" or "netilmicin" or "ototoxic drugs" or "aminoglycosides" or "amikacin" or "dihydrostreptomycin" or "garamycin" or "gentamicin" or "kanamycin" or "neomycin" or "netilmicin" or "streptomycin" or "tobramycin" or "viomycin" or "aminoglycosides as a class of ototoxic drugs" or "cochleotoxic drugs" or "vestibulotoxic drugs" or "antineoplastics" or "carboplatin" or "cisplatin" or "antimitotics" or "antimalarials" or "salicylates" or "loop diuretics" or "quinine" or "streptomycin" or "tobramycin" or "vestibulotoxic drugs") and not "animals") and (toxicity OR toxic OR ototoxic\* OR vestibulotoxic\*)

((MH "Antineoplastic Agents+") or ("loop diuretics") or (MH "Aminoglycosides+") or (MH "Chemotherapy, Cancer") or (MH "Amikacin") or (MH "Bleomycins") or (MH "Carboplatin") or (MH "Chloramphenicol") or (MH "Cisplatin") or ("ethacynic acid") or (MH "Erythromycin+") or "bumetanide" or "vinca alkaloids" or (MH "Furosemide") or (MH "Gentamicins") or (MH "Kanamycin+") or (MH "Methotrexate") or (MH "Neomycin") or (MH "Nitrogen Mustard Compounds+") or (MH "Polymyxin B") or (MH "Colistin") or (MH "Quinine") or (MH "Streptomycin") or (MH "Tobramycin") or (MH "Trimethoprim-Sulfamethoxazole Combination") or ("vinorelbine") or (MH "Vancomycin") or (MH "Vinblastine") or (MH "Vincristine") or ("dactinomycin") or ("dibekacin") or ("difluoromethylornithine") or ("furazolidone") or ("isepamicin") or ("netilmicin") or ("paromomycin") or ("sisomicin")) AND (("vestibulotoxic") or (MH "Ototoxicity"))

("amikacin" or "aminoglycosides" or "amikacin" or "dihydrostreptomycin" or "garamycin" or "gentamicin" or "kanamycin" or "neomycin" or "netilmicin" or "streptomycin" or "tobramycin" or "viomycin" or "aminoglycosides as a class of ototoxic drugs" or "amikacin" or "dihydrostreptomycin" or "garamycin" or "gentamicin" or "kanamycin" or "neomycin" or "netilmicin" or "streptomycin" or "tobramycin" or "viomycin" or "antineoplastics" or "carboplatin" or "cisplatin" or "carboplatin" or "cisplatin" or "cochleotoxic drugs" or "gentamicin" or "kanamycin" or "loop diuretics" or "neomycin" or "netilmicin" or "ototoxic drugs" or "aminoglycosides" or "amikacin" or "dihydrostreptomycin" or "garamycin" or "gentamicin" or "kanamycin" or "neomycin" or "netilmicin" or "streptomycin" or "tobramycin" or "viomycin" or "aminoglycosides as a class of ototoxic drugs" or "cochleotoxic drugs" or "vestibulotoxic drugs" or "antineoplastics" or "carboplatin" or "cisplatin" or "antimitotics" or "antimalarials" or "salicylates" or "loop diuretics" or "quinine" or "streptomycin" or "tobramycin" or "vestibulotoxic drugs")

(vestibulotoxicity OR vestibulotoxic OR ototoxicity OR ototoxic)

TS=(antineoplastic OR aminoglycoside OR chemotherapy OR chemotherapeutic OR loop OR vinca OR amikacin OR bleomycin OR bumetanide OR carboplatin OR chloramphenicol OR cisplatin OR dactinomycin OR dibekacin OR difluoromethylornithine OR erythromycin OR ethacrynic OR furzolidone OR ferosemide OR gentamicin OR isepamicin OR kanamycin OR methotrexate OR netilmicin OR nitrogen OR mustard OR paramycin OR polymysin OR quinine OR sisomicin OR streptomycin OR tobramycin OR trimethoprim-sulfamethoxazole OR vancomycin OR vinblastine OR vincristine OR vinorelbine) AND TS=(ototoxic\* OR vestibulotoxic\*) NOT TS=(mouse OR chinchilla OR pig OR rat OR hamster OR gerbil) AND Language=(English) AND Document Type=(Article OR Review)

MeSH Ear Diseases EXPLODE 1

Ototoxic\* OR vestibulotoxic\*

Antineoplastic OR aminoglycoside OR chemotherapy OR chemotherapeutic OR (loop diuretic) OR (vinca alkaloid) OR amikacin OR bleomycin OR bumetanide OR carboplatin OR chloramphenicol OR cisplatin OR dactinomycin OR difluoromethylornithine OR erythromycin OR ethacrynic OR furazolidone OR furosemide OR gentamicin OR isepamicin OR kanamycin OR methotrexate OR neomycin OR netilmicin OR (nitrogen mustard) OR paromomycin OR polymysin OR quinine OR sisomicin OR streptomycin OR tobramycin OR (trimethoprim sulfamethoxazole) OR vancomycin OR vinblastine OR vincristine OR vinorelbine) AND (ototox\* OR vestibulotox\* OR vestibular OR hearing)

(Ototoxicity OR ototoxic OR ototoxicities OR vestibulotoxicity OR vestibulotoxic OR vestibulotoxicities)AND NOT (animal OR chick OR chicken OR hamster OR rat OR mice OR gerbil OR hamster OR chinchilla OR bird OR fish OR pig OR guinea)

Ototoxic -animal -chick -chicken -hamster -rat -mice -gerbil -hamster -chinchilla -bird -fish -pig -guinea

Vestibulotoxic -animal -chick -chicken -hamster -rat -mice -gerbil -hamster -chinchilla -bird -fish -pig -guinea