NCRAR Workshop

Ototoxicity Early Identification & Monitoring

VA Rehabilitation Research & Development
National Center for Rehabilitative Auditory Research

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VA Medical Center
Portland, Oregon

National Center for Rehabilitative Auditory Research

NCRAR Mission

Alleviate the communicative, social and economic problems resulting from auditory system impairment

Portland, Oregon VA Medical Center

http://www.ncrar.org/home.htm

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Outline

I. Learner Outcomes
II. Overview: Basic Principles
III. Tinnitus Monitoring
IV. Ototoxicity Monitoring in Adults
V. Objective Monitoring
VI. Ototoxicity Monitoring in Children
VII. Establishing Program

I. Learner Outcomes

- Discuss strategies for behavioral & objective monitoring in adults & children
- Discuss approaches for determining objective ototoxic change criteria
- Outline major components for establishing an ototoxicity monitoring program

II. Overview: Basic Principles

Dawn Konrad-Martin, Ph.D
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Ototoxic Medications

Antineoplastic Drugs	*Aminoglycosides*	*Loop Diuretics*
Cisplatin Carboplatin Oxaliplatin Nitrogen mustard Methotrexate* Vincristine Dactinomycin Bleomycin	Gentamicin* Neomycin* Kanamycin Amikacin Streptomycin* Tobramycin* Netilmicin	Furosemide* Ethacrynic acid* Bumetanide*
Other Antibiotics	*Antimalarial Drugs*	*Salicylates*
Vancomycin		

**vestibulotoxic*

Common Uses

- Aminoglycoside antibiotics
  - Gram-negative bacterial infections including those associated with meningitis, wounds, osteomyelitis, tuberculosis and cystic fibrosis
  - In pediatric populations, gentamicin used for medical management of neonates in NICU and tobramicin used to treat cystic fibrosis
- Cisplatin, carboplatin, oxaliplatin
  - Antineoplastic agents used to agressively treat many forms of cancers

Symptoms

- Tinnitus
- Hearing loss
  - Difficulty understanding speech in noise
  - Sensorineural, usually bilateral, symmetric
  - Progresses from high to low frequencies
- Dizziness
  - Dysequilibrium, oscillopsia, vertigo
- Symptoms can be delayed days, months
- Usually permanent, sometimes recovers

Oxidative Mechanisms

Oxidize: Add oxygen, remove hydrogen, or *remove electrons from another compound

Free radicals: Molecules that exist independently having unpaired electrons, energetically unstable, can react with other compounds

Redox Reactions: To stabilize, free radical oxidizes adjacent compound creating a chain reaction

Oxidative Damage: Damage to critical macro-molecules (e.g., DNA, proteins, lipids) causing cell damage, dysfunction or death

Campbell, KC (2003). Ototoxicity: Understanding oxidative mechanisms. JAAA 14, 121-123.

Pathophysiology: AMG

- Hair cell damage & loss
  - Free radical formation (Rotstein & Mandell, 2004; Song & Schact, 1996)
  - Excitotoxic damage (Rostein & Mandell; Roge & Schact, 2000)
- Begins at base (high frequencies), progresses toward apex (lower frequencies)
- First row of OHCs affected first, followed by second and third rows, and then the IHCs (Brockenbrough et al., 2001)

Pathophys: Platinum-based Drugs

- Oxidative Damage (Evans & Halliwell, 1999; Gratton & Smith, 2004; Rybak & Kelly, 2003)
  - Hair cell damage/death
  - Damage to stria vascularis and sprial ganglion cells (Tsukassaki et al., 2000)
- Hair cell damage begins at base, progresses toward apex, first row of OHCs followed by second and third rows, and then the IHCs (Gratton & Smyth, 2004)

Early Identification

- Complaints of ototoxic damage are uncommon until communication problem becomes significant
- Difficult to predict ototoxic damage
  - Relationship to drug dosage, peak serum levels, and other toxicities is variable

Early Identification

Tests sensitive to damage at high-frequencies provide earliest detection (Fausti et al., 1999; Ress et al., 1999)

- Pure-tone thresholds near upper frequency hearing limit (e.g., ultra-high frequency audiometry)
- Evoked otoacoustic emissions (OAEs)
- High-frequency auditory brainstem responses (ABRs)

So What?

Should we care about early changes at the high frequencies enough to take the time to measure them?

Consequences for Communication

- Audibility of consonants critical for understanding speech (De Paoli et al., 1996)
  - Most energy from 2 to 4 kHz
  - 50% of English consonants are fricatives (/v,f,z,s/, etc.) & contain energy through at least 8 kHz
  - /s/ spoken by women & children indistinguishable from /f/, /th/ when energy cut off at 4 kHz (Stelmachowicz et al., 2001)
- Consonants are low in level compared to vowels
  - Unvoiced (/s,p,t,k,th,f,sh/) often below normal thresholds in rapid speech (Northern & Downs, 2002)

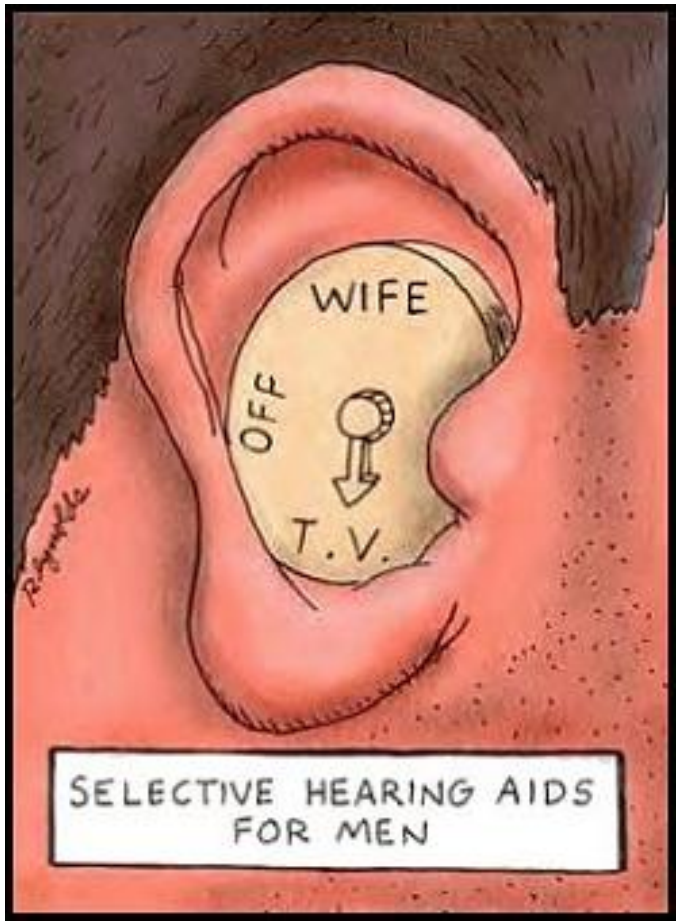
Consequences for Communication

- Audibility from 2 to 9 kHz impacts speech & language of children (Stelmachowicz et al., 2004)

Relevance of Early Identification

- Loss within 2 to 9 kHz range clinically significant for children
- Some impact of high frequency loss on speech understanding, even in adults
- And… hearing aid amplification typically cuts off at 5 kHz
- Moreover, continued damage may affect more of the critical speech frequencies

Prevention is the BEST form of Rehabilitation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SELECTIVE HEARING AIDS
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Rationale for Monitoring

- Early detection may prevent hearing damage that requires amplification/rehabilitation
- If change observed, treatment modification can prevent further hearing loss
- If no change observed, continued treatment warranted
- Provides opportunity for counseling and rehabilitation during and post treatment

Rationale for Monitoring

Informed medical decisions

Target Patient Population

- Receiving highly ototoxic drugs
- Very old & very young people
- Poor medical condition
- Poor renal function
- Poor hydration status
- Familial tendency for susceptibility (aminoglycoside antibiotics)
- Receiving more than one ototoxic drug
- Receiving large or multiple doses

Incidence

- Patient population differences
  - Different risk factors
- Methodological differences
  - Established baseline
  - Criteria for hearing change
  - Frequency range tested
- No standard monitoring techniques

Ototoxic Medications

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Other Antibiotics	*Antimalarial Drugs*	*Salicylates*
Vancomycin See handout	See handout	See handout

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Veteran Study

Hearing loss and tinnitus in large prospective study of ototoxicity

Konrad-Martin D, Phillips DS, Henry JA, Helt WJ, Gordon JS, Deal KM & Fausti SA (2004). Presented at the Association for Research in Otolaryngology. Abstr. 39.

Subjects

- 35 female and 453 male adults (962 ears) seen at one of three VA Participating Sites: VA Medical Centers at Portland, OR; Nashville, TN; and West Los Angeles, CA.
- 2 Groups
  - Adult in-patients and out-patients receiving cisplatin (CDDP group) or carboplatin (Carbo group), or selected aminoglycoside antibiotics or the antibiotic vancomycin (AMG group)
  - Controls were hospitalized patients

Procedures

Baseline Evaluation

(1) Case history, noise exposure and tinnitus history

(2) Otoscopy

(3) Tympanometry

(4) Pure-tone thresholds (0.5 to 8 kHz in 1/2-octave steps and 9 to 20 kHz in 1/6th- octave steps); and

(5) Identification of uppermost frequency with a threshold of $\leq$ 100dB SPL followed by the adjacent six lower frequencies in 1/6th octave steps (SRO).

Procedures

- ***Baseline Recheck.***
  - Repeated pure-tone thresholds within 24 hours or as soon as possible, to determine intersession reliability
  - Subjects excluded if test-retest differences exceeded 5 dB.
- ***Monitor Evaluations***
  - Included (1) tinnitus questionnaire; (2) otoscopy; (3) tympanometry; and (4) puretone thresholds
  - CDDP and Carbo subjects tested w/in 24 hours of each dose
  - AMG and Control subjects monitored every 2 to 3 days throughout treatment course.
- ***Post-treatment Evaluations***
  - ASAP following treatment cessation, and at one, three, and six months following treatment
  - same procedures used as for monitor evaluations

Criteria for Hearing Change

- Subjects served as their own control for hearing change, which was relative to their baseline evaluation.
- Criteria was from ASHA 1994 guidelines:
  - (1) $\geq$ 20 dB change at any one test frequency
  - (2) $\geq$ 10 dB change at any two consecutive test frequencies
  - (3) loss of response at three consecutive test frequencies where responses were previously obtained.
  - Hearing change by any of these criteria was confirmed by retest

Criteria for Tinnitus Onset

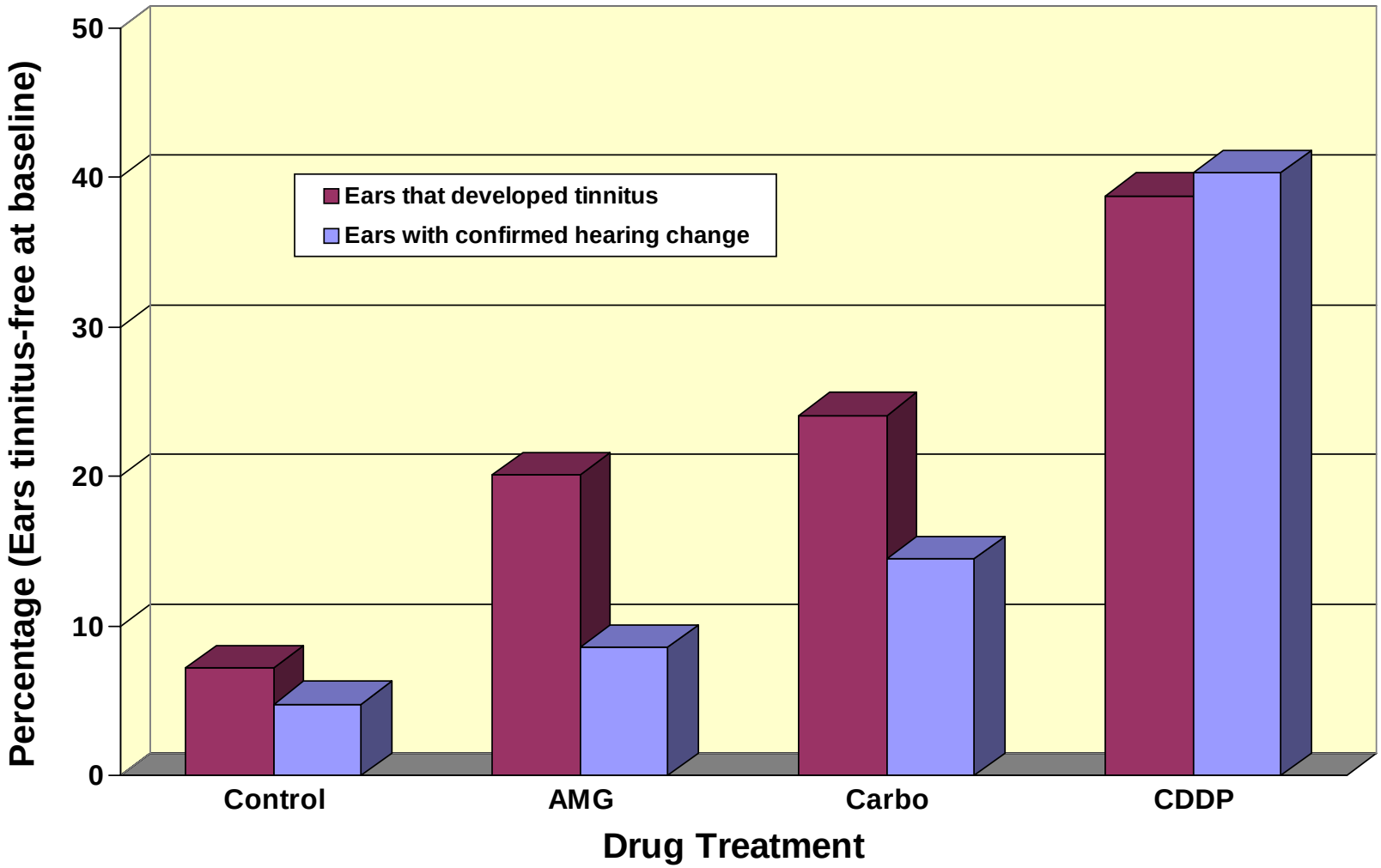
- Analyzed responses to two questions on the tinnitus questionnaire that were repeated at each evaluation
  - (1) Does the subject have tinnitus?
  - (2) If so, in which ear?
- Audiologists administering the questionnaire explained to subjects that an affirmative answer was appropriate when tinnitus was present most of the time, whether it was an intermittent or constant sound

Group Information

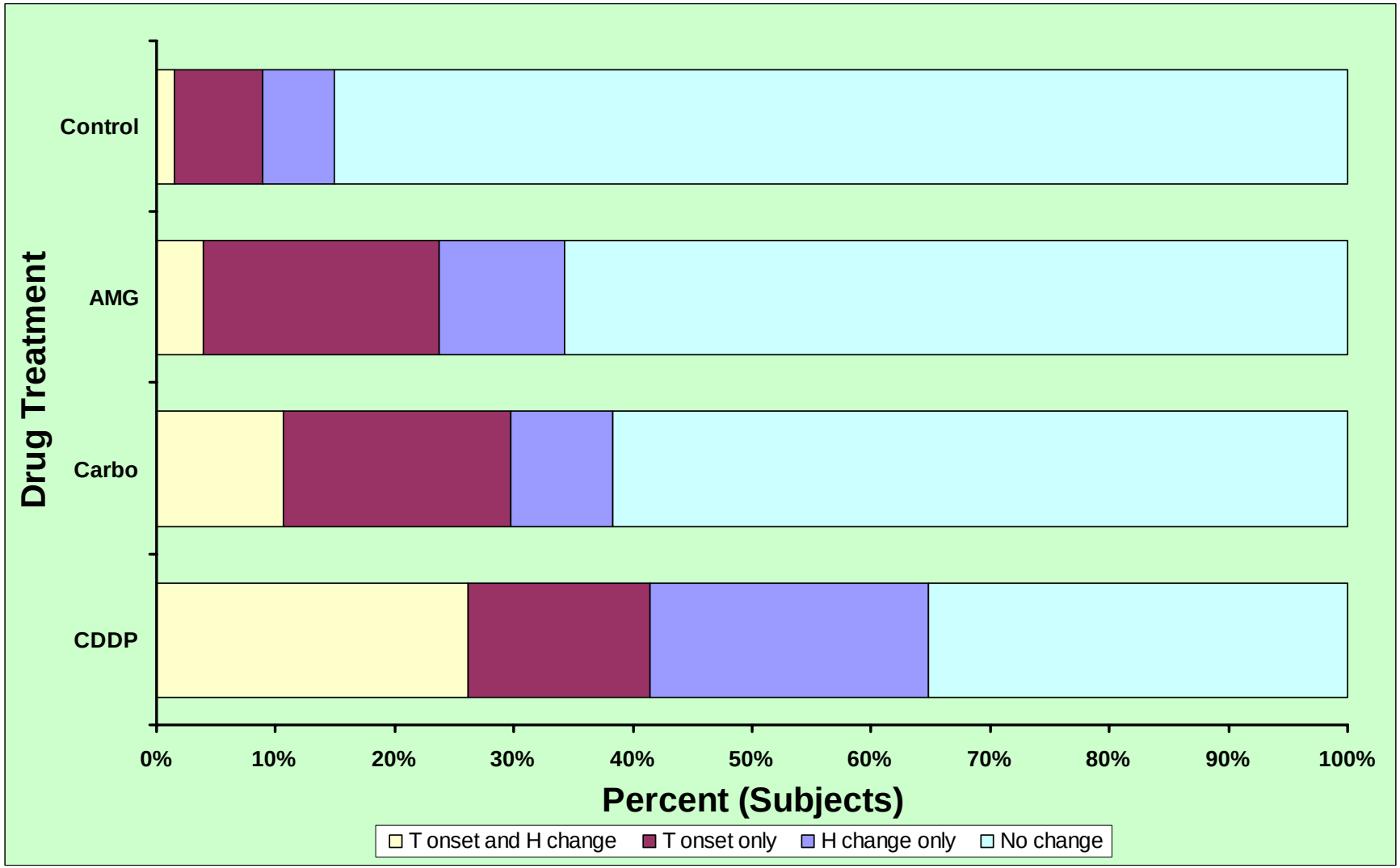
Treatment Group	Baseline	N	% T at Baseline	Age in Years mean (SD)	HF PTA in SPL mean (SD)	Highest Fq in kHz mean (SD)
CDDP	T	162	44%	59.6 (9.2)	43.8 (17.2)	10.6 (3.3)
	No T	206	56%	60.9 (10.6)	38.0 (16.2)	11.3 (3.2)
	Total	***368***		***60.3 (10.0)***	***40.5 (16.9)***	***11.0 (3.3)***
Carbo	T	69	45.4%	64.5 (11.2)	48.4 (17.4)	9.5 (3.6)
	No T	83	54.6%	62.5 (9.1)	38.8 (19.0)	10.5 (3.3)
	Total	***152***		***63.4 (10.1)***	***43.2 (18.8)***	***10.1 (3.4)***
AMG	T	102	42.3%	55.0 (10.8)	39.7 (18.9)	11.9 (3.0)
	No T	139	57.7%	55.7 (10.7)	34.4 (15.1)	10.7 (3.5)
	Total	***241***		***55.3 (10.7)***	***36.6 (17.0)***	***11.4 (3.3)***
Control	T	76	37.8%	54.7 (12.0)	38.3 (19.5)	11.42 (3.4)
	No T	125	62.2%	53.1 (12.3)	30.7 (16.7)	12.3 (3.1)
	Total	***201***		***53.7 (12.1)***	***33.6 (18.1)***	***12.0 (3.3)***
Grand Total	T	409	42.5%	58.5 (11.0)	42.6 (18.4)	10.6 (3.5)
	No T	553	57.5%	57.9 (11.4)	35.5 (16.7)	11.5 (3.2)
	Total	***962***		***58.1 (11.2)***	***39.2 (18.0)***	***11.1 (3.3)***

Subjects free from tinnitus bilaterally at baseline were used to provide evidence for a link between administration of ototoxic drugs and tinnitus

Ototoxic Hearing Change Compared to Tinnitus Onset



Incidence in Veteran Study



Results & Conclusions

- Ototoxic symptoms of tinnitus and/or hearing change occurred in 34% of AMG-, 38% of Carbo-, and 65% of CDDP subjects
- Cisplatin was more ototoxic compared to carboplatin or aminoglycoside antibiotics
- Tinnitus onset and hearing change occurred with similar frequency for cisplatin-treated subjects
- Incidence of tinnitus onset was higher compared to hearing change following carboplatin and aminoglycoside treatment