

Tinnitus: Sensation, Suffering, and Clinical Management

Robert A. Dobie, M.D.
UC-Davis Medical Center

A Clinician's Point of View

- Basic Research Highlights
 - Animal models
 - Mechanisms
 - Imaging
- Clinical Research in More Detail
 - Especially Clinical Trials
- Clinical Management

What is tinnitus?

- An experience of sound that originates in the head of its owner (McFadden), i.e., no external acoustic source
 - Objective (internal acoustic source, activating cochlear partition and at least potentially audible to others...cf. **somatosound**)
 - Subjective (no acoustic source, no cochlear movement, inaudible to others)

“Somatosounds”

- Venous (BIH, hyperdynamic state, jugular bulb or sigmoid sinus anomalies)
- Arterial (carotid anomaly/stenosis, AVM, vascular tumor)
- Non-pulsatile (palatal myoclonus, SOAEs)

What does it sound like?

- Ringing, buzzing, humming, whistling, hissing, roaring, falling water, crickets, etc.
- Meniere's: roaring
- Vascular lesions: pulsatile, **turbulent** (objective)
- But usually quality of tinnitus irrelevant
- Match pitch usually > 3 kHz
- Match intensity usually < 10 dB SL

What causes tinnitus?

- Brief infrequent spontaneous tinnitus?
- Temporary post-noise exposure tinnitus
- Chronic tinnitus
 - Associations with age, SES, sex, noise exposure, general health
 - But primary association is with hearing loss, regardless of otologic disorder
 - Some have tinnitus without hearing loss
 - At least on conventional audiogram

SENSATION
≠
SUFFERING

(see tinnitus pyramid: most people are at the broad base)

“List your problems”

- Getting to sleep (57%)
- Persistence (49%)
- Understanding speech (38%)
- Despair, frustration, depression (36%)
- Annoyance, irritation, can't relax (35%)
- Poor concentration or confusion (33%)
 - Tyler and Baker, 1983

How are tinnitus sufferers different?

Match levels < 10 dB as for non-sufferers

Anxiety disorders (in young)

Depression

- Current
- Lifetime

Suicide

Severely disabled

Moderate ADL interference

Worried about medical implications

Not bothered, forgets about it most of time

Suffering from T: Population Prevalence (Adults)

T “bothers me” > “every few days”: (Cooper, 1994, based on NHANES)	15%
“bothered in last 12 months”: (NHIS, 1990-91)	8.4%
“current, > 3 months” (NHIS, 1994-95)	4.4%
“plagues me all day”: (Axelsson & Ringdahl, 1989)	2.4%
“seriously disturbs life”: (IHR, 1981, Great Britain)	0.5%

Natural history

Retrospective: most patients get worse

Prospective: most patients get better

Both flawed by selection bias

(not population-based)

Prospective studies included at least some counseling

Prognostic factors unknown

Tinnitus is in the Brain

Usually starts with a cochlear lesion....

But:

- Failure of VIII section
- Lidocaine suppression after VIII section
- Contralateral masking at very low levels
- Somatic modulation (68%: R. Levine)

CNS correlates of Tinnitus (and Hearing Loss)

- Auditory nerve: ↓ rate immediately
 - Auditory cortex: ↑ rate (hours)
 - DCN: ↑ rate (days)
- Eggermont (ed. Snow J, 2004)

Imaging Tinnitus

- Several attempts
- Cortex, subcortical regions involved
- Can't yet reliably identify person with tinnitus based on imaging (or any other objective test)

Animal Models of Tinnitus

Many techniques: all based on response to silence!
Most are difficult and time-consuming
Essential to control for HL
Potential: drug trials, mechanistic studies
So far, can model only sensation,
not suffering!

Animal Models and Gabapentin

- Mice with unilateral noise trauma can't detect silent intervals as well as other mice
- Gabapentin restores near-normal detection
- BUT
 - Very small numbers
 - Sensation, not suffering
 - ***2/3 RCTs: negative results!***

Tinnitus Research Consortium

- Established by Robert Wilson (1999)
- Managed by James B. Snow, Jr., M.D.
 - RFAs at www.aro.org
- \$600,000/year in research grants
- 18 refereed papers and chapters
- Stimulus to other non-profits and to NIH
- *Tinnitus: Theory and Management* (2004)

Lessons of TRC

- Animal research is not tinnitus research unless the animal has behaviorally-verified tinnitus.
- No phenomenon should be considered “tinnitus-related” without control for hearing loss.
- Clinical research needs a consensus outcome variable.

Management of tinnitus patient

- Rule out serious or treatable otologic disorder
- Counsel and reassure
- Look for contributing factors (musculoskeletal, psychological, drugs)
- Consider hearing aids
- Consider sleep management (including bedside masking)
- Consider other treatments.....?

Unilateral tinnitus workup

Based on associated findings (hearing asymmetry, pulsatile vs. non-pulsatile, physical exam), may need:

MRI
CT
Angiography (CT, MR, intra-arterial)
ABR

Goals of treatment

- Eliminate tinnitus sensation
- Reduce tinnitus sensation
 - Worthwhile only if suffering reduced
- Reduce/eliminate tinnitus suffering
- Outcomes should be measured in terms of suffering, whether treatment is directed at sensation or suffering
- No consensus yet on outcome measures

RCTs for tinnitus

- Necessary because of ignorance of natural history and prognostic factors
 - Exception: if treatment found that could frequently eliminate tinnitus
- Easy to do because tinnitus is common and somewhat stable
- No treatment shown to provide long-term benefit (Dobie, Laryngoscope, 1999)

Dissecting Treatment X

- Drug? Caring people? Trust? Outing?
- Placebo (inert substance)
- Blinding (to preserve other elements)
- “Placebo effect” not from the placebo!
- Why do we care?
 - Costs and risks
 - Future research

Review of RCTs for Tinnitus

- Excluded
 - tinnitus as treatment side effect
 - specific disorders, e.g., Meniere's
 - IV lidocaine
 - waiting list controls
- 69 RCTs from 1980 - 1998
 - Laryngoscope, August 1999
- 5 added in 2002
- 4 added in 2004

Deficiencies of Tinnitus RCTs

- Specific studies
 - Small samples (low power)
 - Failure to follow post-hoc leads (subgroups)
 - Short follow-up
- The field
 - No staging system
 - No consensus outcome measures
 - Placebos difficult for non-drug therapies

Problems with Tinnitus RCTs

False positives

Waiting list controls (amylobarbitone, psychological Rx)
Unequal treatment (Xanax)
Unblinding by side effects (Xanax)
Statistical fishing trip (CBT vs. yoga)
Unconvincing placebo (biofeedback, massage)
Statistical errors (ginkgo)

Problems with Tinnitus RCTs

False negatives

N too small (e.g., melatonin)
Crossover can help
Inclusion of mild cases (trimipramine)
Heterogeneity (almost all studies)
Open trials can help
Non-placebo (Benadryl vs. Valium, etc.)

Pills that may help

Tricyclics (e.g., Nortriptyline; Dobie, 1993)
especially if sleep interference
global benefit: 67% vs. 40%
Paroxetine (Paxil; Robinson, in Snow, 2004)
non-depressed, able to tolerate 50 mg/d
Alprazolam (Xanax)?
Cyclandelate (Cyclospasmol)?
Zinc in zinc deficiency?

Drugs that probably don't help

Tocainide
Topical lidocaine
Carbamazepine (Tegretol)
Ginkgo
Baclofen, Lamotrigine, Misoprostal,
Nicotinamide, Betahistine, Cinnizarine,
Flunarizine, Caroverine, Eperisone,
Melatonin, Gabapentin

Possibly Worth More Study

- Cyclandelate, Xanax, Eperisone (measured sensation)
- Flunarizine (subgroup with dizziness)
- Caroverine (conflicting results)
- Melatonin (subgroup with sleep problems)

Placebos for Non-Drug Therapies

- Inactive devices (electrical stimulation)
- “Wrong” methods
 - Tyler TRT/noise level trial
 - sham acupuncture
 - can be difficult to blind therapist
- Perhaps unnecessary if risks negligible

Placebo-controlled RCTs: Non-Drug

- Magnetic stimulation (ineffective)
- Ultrasound (ineffective)
- Biofeedback (mixed results, poor blinding)
- Acupuncture (ineffective)
- Laser (ineffective)
- Masking (small benefits)
- Electrical Stimulation (rarely effective)

Non-Drug RCTs Without Placebos

- Two or more treatments compared
 - Hypnosis
 - Counseling
 - Cognitive therapy
 - Behavioral therapy
 - Relaxation
 - Yoga

Non-drug treatments that may help

Wearable masking devices (low % use)
Psychotherapy (talking)
Includes brief unhurried counseling
Relaxation, reassurance, distraction, cognitive/behavioral, education, problem-solving
TRT = psychotherapy plus device

Non-drug treatments that probably don't help

Acupuncture
Magnetic stimulation
Laser stimulation
Ultrasound
Biofeedback, massage
TMD treatment in the absence of TMD
Hypnosis
Botulinum toxin injections

Counseling for Mild Tinnitus

- Tinnitus is common
- CNS (brain, not mind) reaction to cochlear cell loss (phantom limb analogy)
- Not dangerous (assumes previous medical workup)
- Prognosis is good

Which type of psychotherapy?

“Everyone has won and all must have prizes” (Alice in Wonderland)

No meaningful, persistent differences when intensity of interaction held constant

Referral based on availability, cost, and belief – but should be rare

Conclusion (1999)

- “None of the treatments studied to date has been shown ... to provide replicable long-term reduction in the impact of tinnitus on everyday life in excess of placebo effects.”
- BUT unquestionable value of “placebo”
 - attentive, complete workup
 - unhurried explanation and discussion of options
 - reassurance, availability, follow-up

What have we learned?

- How to do clinical trials for tinnitus
 - Double-blind, placebo-controlled, randomized
 - Increase statistical power (sample size, open trials, selection criteria, crossover design)
 - Need staging, consensus outcome measures
- There is no standard of care, but drugs that work in the brain are promising

Conclusions

- Tinnitus RCTs suggest short-term benefit:
 - Tricyclic antidepressants
 - possibly Xanax, electrical stimulation
- Many RCTs suffer from poor design
- Consensus staging and outcome measurement needed
 - for RCTs
 - for cost-effectiveness studies

Conclusions

Sensation (associated with hearing loss)
Suffering (psychological factors)
Essential to rule out serious disease
No consensus re prognostic factors, outcome measurement
Counseling, hearing aids, sleep mgmt.
Detect depression
Refer rarely