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Tinnitus Update

2009 Missouri Academy of Audiology Meeting
September 18, 2009

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Financial Disclosure

- NIH Grant Support
Learner Objectives

- Understand current concepts of the etiology of tinnitus
- Understand current concepts behind new therapeutic initiatives
- Understand new imaging techniques for tinnitus
Collaborative Research Team at Washington University

- Dr. Keith Garcia, Psychiatry
- Dr. Kathy Pierce, Psychiatry
- Dr. Mark Mintun, Neuroimaging
- Dr. Harold Burton, Neuroanatomy
- Dr. Stephen Duntley, Neurology
- Dianne Duddy, Audiology
- Joyce Nicklaus, Research Coordinator
Challenges to tinnitus research

- Identifying characteristics of tinnitus patients that may predict a positive response to a particular therapy
- Lack of “objective” measure
- Chronic tinnitus is likely a heterogeneous condition for which there is no universally effective treatment
- Time of initiation of therapy relative to onset
- Placebo effect
- Multiple endpoints
- Dropouts
- Long-term results
- Psychological overtones
Etiology

- Recent research favors the theory of discordant damage or dysfunction of OHC and inner hair cell (IHC) systems proposed in 1990.

- Hypothesis postulates that tinnitus-related neuronal activity is generated in the dorsal cochlear nucleus as a result of unbalanced activity transmitted by type I and type II auditory nerve fibers.

Jastreboff Neurosci Res 1990;8:221-54
Kaltenbach et al J Neurophysiolo 2002;88:699-714
When OHC are damaged or dysfunctional, while inner hair cells are reasonably intact, activity in type I fibers is normal, while activity in type II fibers is absent or decreased.

The discordant dysfunction theory may provide explanation to a number of questions regarding tinnitus:
- why 20% of tinnitus patients have normal hearing
- why tinnitus is absent in 27% of totally deaf people

Jastereboff, in Mechanisms of Tinnitus, Boston 1995, p 73-94
- Tinnitus severity is not related to the psychoacoustical characteristics of tinnitus, and treatment outcomes cannot be predicted by psychoacoustical measures.
- Support the postulate that the effects of tinnitus on an individual depend on the extent of activation of the limbic and autonomic nervous systems and not on the level of activation within the auditory pathways.
Integrative Model of Developing Tinnitus


- Cochlea
  Dysfunction of hair cells after damage

- Auditory Nerve
  Dysfunctional physiological pattern

- Brain stem
  Dysfunctional thalamocortical signal cycles, somato-otic interactions

- Auditory cortex
  Plasticity – Tonotopic re-organisation

- Limbic system
  Emotional and cognitive processing and enhancement

- Generation
- Chronic
- Decompensation
"The ringing in your ears—I think I can help."
Challenges in Tinnitus Therapy

- Chronic tinnitus is likely a heterogeneous condition for which there is no *universally* effective treatment.
- Identify characteristics of tinnitus patients that may predict a positive response to a particular therapy.
- Time of initiation of therapy relative to onset.
- Placebo effect/psychological overtones.
- Multiple endpoints – loudness vs. suffering, QOL.
Some Things We Think We Know

- Dobie (1999) performed systematic review of the literature of randomized clinical trials of various drugs, psychotherapy, maskers, acupuncture, hypnosis, and other treatments.
- He concluded that none of the treatments were able to eliminate tinnitus more frequently than placebo, or even to provide replicable long-term reduction in the impact of tinnitus in everyday life.

Antianxiety, antidepressants, and hypnotics found to provide significant relief

Patients benefited from a non-specific (placebo) therapy described as clinician contact, recognition of their problem, and assurance of a benign nature
Benzodiazepines

- Diazepam (Valium) and alprazolam (Xanax)

- Johnson et al (1993) RCT Alprazolam vs Placebo
  - Tinnitus loudness was reduced

- Serious potential for dependency and abuse

Antidepressants

- 4 randomized clinical trials identified
- Three of the 4 studies showed statistical difference in subjective tinnitus
- Amitriptyline and nortriptyline shown to be effective
- Effect may be greater when there is sleep disturbance

Bayar J Otolaryngol 2001;30:300-3
Podoshin et al Int Tinnitus J 1995;1:54-60
Newer Antidepressants

- Serotonin reuptake inhibitors (SSRI)
  - Sertraline (Zoloft)
  - Paroxetine (Paxil)
  - Escitalopram (Lexapro)
  - Fluoxetine (Prozac)
  - Bupropion (Wellbutrin)

- Robinson et al (2005) conducted double-blind placebo-controlled trial of paroxetine
  - Results ambiguous; better with higher dosage

Robinson *Psychosomatic Medicine* 2005; 67:981-988
Gabapentin (Neurontin®)

- Structurally related to the neurotransmitter GABA – inhibitory neurotransmitter
  - Does not interact with GABA receptors
  - Is not converted metabolically into GABA or a GABA agonist
  - Is not an inhibitor of GABA uptake or degradation

- Preclinical studies documented an analgesic effect

- Reduce spontaneous pain in patients with peripheral or central pain
Case Report

- Patient presented to a chronic pain clinic with a 10-month history of tinnitus
- Prescribed a 2-week course of gabapentin and amitriptyline
- Within 24 hours of starting gabapentin, the patient's tinnitus ceased
- However, after two weeks, the patient's supply of gabapentin was depleted and his tinnitus immediately returned
- The patient was restarted on gabapentin and remained tinnitus free for over two years

Zapp JJ. *Ear, Nose, & Throat Journal* 2001;80:114-116
Animal Model

- Bauer et al developed an animal psychophysical model to reflect several features of tinnitus observed in humans and to test the impact of gabapentin.

- Chronic tinnitus was induced in rats by a single intense unilateral exposure to noise.

- Tinnitus was reversibly attenuated by treatment with gabapentin.

  Bauer and Brozoski. *JARO* 2001;2:54-64
Clinical Trial

- Placebo-controlled single-blind clinical trial of 39 patients divided into two cohorts of adult patients with tinnitus — those with and those without evidence of acoustical trauma.
- No significant overall effect of gabapentin on psychoacoustic tinnitus loudness or THQ responses in either cohort of patients with tinnitus.

Bauer CA, Brozoski TJ. Laryngoscope 2006;116:675-681
Washington University Clinical Trial

- NIH-sponsored randomized placebo-controlled double-blind study to assess therapeutic benefit of gabapentin for subjective idiopathic troublesome tinnitus
- Enrolled 115 subjects
- Primary outcome measure was Tinnitus Handicap Inventory
- Trial Began May 2004 and ended February 2006

Piccirillo Arch Otolaryngol Head Neck 2007;133(4):390-397
Baseline Assessment

- Demographic
- Clinical
- Audiometric
- Patient-Based
  - Tinnitus Handicap Inventory (THI)
  - Brief Symptom Inventory (BSI)
  - Beck Depression Inventory (BDI)
  - Epworth Sleepiness Scale (BSI)
**Titration Period (Baseline – Week 4)**

Gabapentin or placebo were supplied to patients in 4 separate vials (300 mg per capsule)

- Week 1 900 mg/d
- Week 2 1800 mg/d
- Week 3 2700 mg/d
- Week 4 3600 mg/d
THI as a Function of Treatment Assignment

Time of Assessment

THI Baseline  THI 4 Weeks  THI 8 Weeks

THI Score (Out of 100)

Gabapentin
Placebo

0  10  20  30  40  50  60
Primary Outcome Measure

The change in THI between Baseline and Week 8

Overall  N=109, Δ 10.83

Gabapentin  N= 55, Δ 11.06
Placebo  N=54, Δ 10.61

Δ THI between Gabapentin and Placebo
0.45 95% CI -5.71 to 6.59

Before the study, we decided that a 10-point difference in the change in THI (Baseline to Week 8) between gabapentin and placebo would be clinically significant.
“Considering your experience with tinnitus at the start of this study, how would you rate the change in the severity of your tinnitus at this time?”

Very Much Worse = 0
Somewhat Worse = 1
Minimally Worse = 2
No Change = 3
Minimally Better = 4
Somewhat Better = 5
Very Much Better = 6

- Overall 2.91
- Gabapentin 2.96
- Placebo 2.85
- Difference 0.11
  95% CI - 0.26 to 0.49
Melatonin

- Melatonin is a hormone involved in regulating the sleep-wake cycle
- Rosenberg (1998) et al. evaluated the effects of melatonin vs placebo
  - Found no improvement in tinnitus
  - Found improvement in sleep
Washington University Clinical Trial

- Prospective open-label study of 20 patients with tinnitus
- Patients took 3 mg of melatonin per day for 4 weeks; followed by 4 weeks of observation
- THI and Pittsburgh Sleep Quality Index (PSQI)
  - Week 2
  - Week 4
  - Week 6
  - Week 8

Megwalu Otolaryngol Head Neck 2006;134:210-213
### THI and PSQI Values at Weeks 0, 4, and 8

<table>
<thead>
<tr>
<th>Variable</th>
<th>Week 0</th>
<th>Week 4</th>
<th>Week 8</th>
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<tbody>
<tr>
<td>THI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>20</td>
<td>20</td>
<td>18</td>
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<tr>
<td>mean</td>
<td>35.4</td>
<td>28.8</td>
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<td>95% CI</td>
<td>29.1 to 41.5</td>
<td>19.6 to 38.0</td>
<td>16.7 to 33.3</td>
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<tr>
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<td>31.0</td>
<td>24.0</td>
<td>21.0</td>
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<tr>
<td>PSQI</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>mean</td>
<td>7.9</td>
<td>5.0</td>
<td>5.5</td>
</tr>
<tr>
<td>95% CI</td>
<td>5.9 to 9.9</td>
<td>3.3 to 6.7</td>
<td>3.3 to 7.7</td>
</tr>
<tr>
<td>median</td>
<td>6.0</td>
<td>4.0</td>
<td>4.5</td>
</tr>
</tbody>
</table>
- THI scores improved after taking melatonin
- PSQI scores improved after taking melatonin
- The improvement in tinnitus was found to be associated with improvement in sleep
- The impact of melatonin on sleep was greatest among patients with the worst sleep quality
- The impact of melatonin on tinnitus was not associated with the severity of the tinnitus
Acamprosate (Campral®)

- NMDA-receptor antagonist that protects the glutamatergic system from pathological activation and regulates GABA-ergic transmission
- Thought to reduce the pleasurable effects of alcohol ingestion
- Helps patient maintain abstinence until adequate self-motivation for abstinence has been established
Acamprosate (Campral®)

- Acamprosate has been studied extensively in Europe and appears to be quite helpful and to have no major adverse effects.

- Although the mechanism underlying CNS effect(s) is(are) still being investigated, it appears that acamprosate interacts with the GABA (inhibitory) and glutamate (excitatory) systems.

- Underlying theory suggest that tinnitus is caused by disruption in the same pathways that are involved in addiction to alcohol.
Aparecida et al. (2006) conducted a double-blind, placebo-controlled clinical trial to assess the therapeutic effectiveness of acamprosate on subjective idiopathic tinnitus.

- 50 patients were divided into two groups: 25 received acamprosate, and 25 received placebo for a period of three months.

- Patients’ rated their change in tinnitus using a subjective scale from 1 to 10.

- 87% of the patients in the acamprosate group reported a drastic change in their tinnitus.

- Incidence of side effects was low at 12% and all of them were mild.
Initial ≠ 30d ≠ 60d ≠ 90d

Tinnitus Scale (media ± SD)

Acamprosato

Placebo

p = 0.22

p < 0.0001
Medication Trials Listed on Clinicaltrials.gov

- Zinc
- Neramexane
- Modafinil
- Deanxit and Clonazepam
Psychological Treatments

- Andersson and Lyttkens (1999) performed meta-analysis of psychological treatment of tinnitus
- 18 studies > 700 subjects
- Studies included cognitive/cognitive-behavioral treatment, relaxation, hypnosis, biofeedback, educational sessions, and problem solving
- Conclusion -- Psychological treatment for tinnitus is effective, but aspects such as depression and sleep problems may need to be targeted in future studies

**Masking Devices**

- Anecdotally, many patients sleep better with masking devices
- May be combined with hearing aids
- Erlandsson (1987) conducted RCT masking vs placebo
  - Small but statistically significant effect
- Patients with hearing loss seem to prefer hearing aids over masking devices

Electrical Stimulation

- Current delivered to electrodes in or near cochlea can suppress tinnitus sensation
- Wearable electrical devices in the 1980s
- Two randomized clinical trials failed to show improvement
- Two studies with intriguing result – single patients who repeatedly and reliably showed strong tinnitus suppression when device was on but not when it was off
Tinnitus Retraining Therapy

- TRT aims to habituate tinnitus signal and relieve decreased sound tolerance
- Multiple studies seem promising
- After successful TRT, patients can still hear tinnitus when they focus, but tinnitus doesn’t affect QOL
- Large scale NIH-supported RCT underway
Goal of TRT

- Achieve habituation of reaction, which is the weakening and disappearance of functional connections between the auditory pathways, and the limbic/autonomic nervous systems.
- In this case, patients may still perceive tinnitus, however, they are not bothered by it.
TRT- Direct Counseling

- All patients undergo retraining counseling tailored to their specific category of tinnitus
- Six specific points discussed during the retraining counseling

Jastreboff and Jastreboff Otolaryngol Clinics NA 2003;36:321-336
1. There is no medical problem which can be linked to tinnitus, and our evaluation assured that this is a case.

2. Tinnitus is not a real sound: it is perception of neural activity, and as such, it is governed by different principles than activity evoked by sounds.

3. Tinnitus-related neuronal activity is a weak signal and its impact on the patient’s life depends on the brain’s interpretation of this signal.
4. It is impossible at present to repair a damaged cochlea, however, it is possible to modify the way the brain detects and responds to the signal by retraining of neural connections.

5. The brain is a very plastic organ and undergoes constant functional reconfiguration. It is possible to train the brain to filter out the signal, and thus, prevent it from activating the limbic and autonomic nervous systems.
6. There is no relationship between tinnitus and progressive hearing loss; tinnitus does not cause hearing loss, and hearing loss does not cause tinnitus, despite the fact that tinnitus is more prevalent in people with hearing loss.
Sound Therapy

- Sound therapy is implemented by using a tabletop sound machine and a wearable sound generator, which is set at "mixing" or "blending" point.
- At this level, patients can still perceive separately tinnitus and sound from the sound generators, but these two perceptions start to intertwine, interact, blend, and mix together. Sound generators are used as long as possible during the waking hours and the level of sound stays the same throughout the day.
Outcomes

- There are no published randomized, well-controlled studies evaluating the effectiveness of TRT.
- There is a growing number of clinical reports documenting the effectiveness of this method.
- With the present version of TRT, tinnitus improvement is usually seen at the third month.
McKinney et al

- Longitudinal observational study
- Enrolled 186 patients
- Divided the cohort into 6 subgroups based on hearing status and need for hearing aids
- Outcomes – psychoacoustic measures and questionnaire data
- 72% DC, 67% DC + LLNG, 83% Full TRT demonstrated 40% or greater improvement

McKinney et al Proceedings 6th Int. Tinnitus Seminar (p.99-105), London, UK
Herraiz et al

- Compared efficacy of TRT with that obtained for tinnitus patients receiving partial TRT (without sound therapy) and improvements obtained for control patients on waiting list
- Prospective, non-randomized clinical essay
- Primary finding – 82% of patients who received full TRT reduced their THI scores by 16% (statistically significant)

Conducted pilot study

Randomized ~60 patients to
- Full TRT
- DC and complete noise masking of tinnitus via noise generators
- DC alone

Patients evaluated at 12 and 18 months

~80% reduction in tinnitus handicap in all groups

Henry et al

- Controlled prospective study
- 124 veterans with severe tinnitus
  - TRT
  - Masking treatment
- Tinnitus Severity Index and THI, THQ
- Each group experienced
  - Similar improvements at 6 months
  - TRT significantly greater improvement at 12 and 18
- Improvements greatest for most severe patients

"We located the hissing noise, Mr. Watkins. Your wife's mother is in the back seat."
Neuromonics Tinnitus Treatment

- Intention of simultaneously addressing the auditory, attentional, and emotional processes
- Involves use of a medical device for daily, at-home administration of an acoustic treatment, together with a comprehensive education, counseling, and support program that typically involves six face-to-face appointments with clinician over a 6-month period
**Auditory**

1. **Perception**
   - Hearing loss / auditory damage
   - Adaptive response: changes in neuronal activity + sensitivity in auditory system
   - Altered neural activity interpreted by auditory cortex as sound

2. **Attention**
   - Neural filters identify patterns in auditory pathways
   - Significance placed on perceived tinnitus sound
   - Brought to conscious attention
   - Leads to awareness of tinnitus sound

3. **Reaction**
   - Autonomic nervous system causes ‘fight or flight’ stress response
   - Leads to disturbance + reinforces auditory sensitivity
   - Amygdala reinforces filter significance
   - Leads to ‘vicious cycle’

---

**Stimulation**
- Wide-frequency acoustic stimulus
- Customized for each patient’s hearing profile (binaural, stereo)

**Desensitization**
- Intermittent interaction with tinnitus perception (dynamic stimulus)
- Graded increase in exposure, while relaxed

**Relaxation & Relief**
- Pleasant, relaxing music
- Relief from tinnitus perception/annoyance
- Counseling / support
- Individually prescribed acoustic stimulus, which provides a broad frequency stimulus
- Addresses the effects of auditory deprivation, promotes relief and relaxation with the intention of reducing engagement of the amygdala and autonomic nervous system
- Applies the principles of systematic desensitization to address the attentional processes
Involves use of an acoustic stimulus that is customized by spectral modification to account for each patient’s hearing loss profile and administered in a manner that is tailored to his or her tinnitus profile.

This is complemented with a counseling and support program that is collaboratively tailored to the specific needs of each individual.

By customizing the treatment in this way, its effectiveness, efficiency, and user acceptability are maximized.
- Patients initially use their customized treatment for 2 or more hours per day
- The acoustic stimulus is provided to patients via a proprietary, purpose-built medical device
- It includes features such as treatment dosage monitoring/reporting tools that facilitate compliant usage, as well as volume controls that encourage appropriate setting of volume
The treatment also involves a structured rehabilitation program, typically provided over a 6-month period by a clinician specifically trained in tinnitus treatment.

This program encompasses a comprehensive suite of elements:

- education concerning tinnitus and how it can be addressed
- coaching and behavioral modification addressing such aspects as relaxation, sleep management
- reduction in exposure to factors that may exacerbate tinnitus
- counseling to address any cognitive distortions relating to tinnitus and to assist with management of the emotional response to it
- monitoring of progress through measurement and feedback of various measures of tinnitus symptoms
How the Neuromonics Tinnitus Treatment Addresses the Neurological Processes Underlying Clinically Significant Tinnitus

- Auditory Stimulation to Address the Effects of Auditory Deprivation
- Relaxation and Relief to Address the Aversive Reaction/Stress Response
- Systematic Desensitization to Address the Perceptual Filters That Lead to Attention to the Tinnitus
Acupuncture

- Effectiveness?
- Dobie (2004) Multiple studies suggest that acupuncture performed “the wrong way” works as well as acupuncture performed “correctly”
Patented treatment method based on sound cancellation principles

Fundamentally different from all other tinnitus treatments currently available

Therapy designed to address predominant-tone tinnitus

Listen to the therapeutic sound pattern through headphones for 30 minutes, three times a week
Intratympanic Steroid Treatment

Synthetic glucocorticoids used as anti-inflammatory or immunosuppressive agents

- Dexamethasone
- Methylprednisolone
- Betamethasone
Methods of Delivery

- Single Injection
Methods of Delivery

- Self Administering Drops
Intratympanic dexamethasone treatment for control of subjective idiopathic tinnitus

- 50 patients with subjective tinnitus
- 4 mg of dexamethasone, three-times daily for 3 months
- 17 patients (34%) reported no tinnitus after treatment
- 20 patients (40%) reported a significant decrease
- 13 patients (26%) reported no effect
Intratympanic Steroid Treatment

- 50 patients with subjective tinnitus
- 4 mg of dexamethasone, three-times daily for 3 months

Cessarini et al. *Int Tinnitus J* (2002) 8(2);111-114
- 17 patients (34%) reported no tinnitus after treatment
- 20 patients (40%) reported a significant decrease
- 13 patients (26%) reported no effect
**Electrical Stimulation**

- Current delivered to electrodes in or near cochlea can suppress tinnitus sensation
- Wearable electrical device in the 1980s
- 2 RCTs failed to show improvement
- Two studies showed intriguing result – single patients who repeatedly and reliably showed strong tinnitus suppression when device was on but not when it was off

**Problems**
- Are the results seen in individual patients repeatable
- Does stimulus have effect on acoustic thresholds
Repetitive Transcranial Magnetic Stimulation (rTMS)

- TMS Therapy involves the use of very short pulses of magnetic energy to stimulate nerve cells in the brain.

- The unique nature of magnetic fields allows them to pass through the skull and into the cortex without being distorted in any way.

- This facilitates a very focal type of stimulation, minimizing stimulation of brain tissue not involved in the area being treated.
Repetitive Transcranial Magnetic Stimulation (rTMS)

- Once inside the brain, the rapidly changing nature of the magnetic pulses induces electrical charges to flow.

- The amount of electricity created in the brain is very small, and can not be felt by the patient.

- When in the correct orientation relative to brain cells (neurons) these very small electric charges can cause the neurons to fire or become active.

- The objective of TMS Therapy is to stimulate (or activate) brain cells.
Repetitive Transcranial Magnetic Stimulation (rTMS)

- Patients remain awake and alert during rTMS
- Once the treatment is done the patient is free to return to work or to normal activities
rTMS and Tinnitus

- Variety of investigators have studied the effects of rTMS on tinnitus
- Low-frequency (1 Hz) rTMS applied to the scalp overlying the region of the primary and secondary auditory cortex can reduce tinnitus severity
- Shallow penetration of rTMS stimulation suggest that rTMS stimulation is unlikely to have an effect on the primary auditory cortex
Goal of rTMS for Tinnitus

- Interrupt tinnitus perception
- Induce a process of synaptic plasticity generating long-term synaptic depression with the aim of reducing tinnitus-associated hyperactivity
PET and MRI-guided neuronavigated 1 Hz rTMS to auditory cortex

10 patients

All PET scans showed increased activity PAC

Placebo-controlled cross-over study

110% motor threshold; 2000 stimuli/day for 5 days

“Remarkable” improvement after 5 days

No serious adverse of side effects
Sham, cross-over

Studied 3 patients

Used PET to identify area of increased cerebral metabolic activity in primary auditory cortex in 2 patients

Selective stimulation of left TPC with low-frequency rTMS resulted in considerable improvement
Plewnia et al

- Demonstrated transient moderate suppression
- High-frequency (10 Hz) to 8 scalp and 4 control positions in 14 patients with chronic tinnitus
- Responding subjects described tinnitus suppression after rTMS as a new and surprising experience

Plewnia et al Annals Neurol. 2003;53:263-266
Langguth et al

- 10 chronic patients; all underwent PET and MRI
- Increased activity identified in primary auditory cortex
- Low-frequency rTMS directed at area of increased activity
- Moderate improvement noted
- Improvement lasted for 6 months in 6 patients

Langguth et al Biol Neuropsych 2004;31:S52-S54
DeRidder et al

- Retrospective analysis of rTMS for 114 patients
- 90% motor threshold
- 1, 3, 5, 10, and 20 Hz
- Outcome
  - Good effect 25%
  - Partial effect 28%
  - No effect 47%
  - Effect very short lasting

DeRidder et al Otol Neurotology 2005;26:616-619
Londero et al

- 13 subjects
- Low-frequency stimulation PAC contralateral to tinnitus; area of maximal fMRI activation
- 120% MT
- 5 responders to active stimulation; 1 responder to control

Londero et al. Neurophysiol Clinic 2006;36:145-155
Plewnia et al

- 2 weeks rTMS targeted to tinnitus-related increase in regional cerebral blood flow
- 6 subjects
- Low-frequency active or sham to targeted area
- 5 of 6 patients, rTMS induced greater reduction of patient-reported tinnitus distress
- 1 reported tinnitus as greatly improved, 1 reported improved
- Tinnitus returned to baseline within 2 weeks in all but one patient

Plewnia et al J Neurol, Neurosurg, Psych. 2007;78:152-156
Rossie et al

- Randomized, double-blind crossover, placebo controlled
- 16 patients with chronic tinnitus
- Low-freq, 120% motor threshold; 5 days; L TPC
- 8/14 “responders”; 2 developed worse tinnitus
- Active rTMS induced overall significant, but transient improvement

Rossie et al. J Neurol, Neurosurg, Psych. 2007; 78:857-863
Our Thoughts

- These treatment protocols weren’t very aggressive
- No lasting improvement
- This research parallels depression literature
  - Early studies based on under treatment (low intensity, short duration) showed transient improvement in mood but results not durable or robust
  - Recent studies demonstrate efficacy with more aggressive protocols
Although rTMS appears to be a very promising tool for the diagnosis and treatment of tinnitus patients, available knowledge is still very limited at the moment. Further basic research and clinical studies are needed in order to optimize the parameters of stimulation (stimulus frequency, cortical target definition) and to validate the application of this technique in the management of patients with disabling tinnitus.

Londero et al Neurophysiologie Clinique 2006; 36:145-155
Current Clinical Trial

- Study Design: Randomized, Double Blind, Placebo Control, Crossover Assignment, Safety/Efficacy Study
  - Neuronetics Model 2100 CRS rTMS System
  - Half of the participants are randomly assigned to start with sham rTMS for 2 weeks and then switch to active rTMS for 2 weeks; the other half will receive the opposite assignment.
  - For the washout period between the two interventions, we will plan a minimum of 2 weeks to avoid the problem of carryover effects.
- Subjects: Men and women between the ages of 18 and 60 years; Subjective, unilateral or bilateral, non-pulsatile tinnitus of 6 month's duration or greater; and Tinnitus Handicap Inventory score of 38 or greater.

Clinical Trials.gov Identifier:NCT00567892
Stimulation Settings

- Frequency -- 1Hz on 330 sec (5 min 30 sec.) per train for the first 5 trains with the last train 350 sec. (5 min. 50 sec.) in duration
  Off -- 90 sec (1 min. 30 sec.)
- Intensity -- 110% of motor threshold
- Duration -- 42½ minutes (total 2000 pulses in 6 trains)
Sham Comparator appears identical to and mimics sounds and sensations of active magnet.
Outcome Measure

- Primary outcome measure is defined as the change in the THI score between active rTMS and sham rTMS

- Secondary outcome measures
  - Patient Global Impression of Change
  - Participants asked if they would
    - Continue treatment
    - Recommend this treatment to a friend.
Functional Connectivity MRI

Left Auditory Seed

n = 13
Functional Connectivity MRI

Left Auditory Seed

BASELINE  Group t-maps  rTMS TREATMENT

n = 13  n = 12

-.05  -.005
Statistically significant (paired two-tailed t-test, n=12, p < 0.01) differences between Tinnitus baseline and after rTMS treatment.

**[18F] PDG PET**

- **L Hippocampal**
- **L Caudate**
- **Anterior Cingulate**
- **Auditory cortex (No Changes)**

Coordinates:
- L Hippocampal: -23 -17 -14
- Anterior Cingulate: 5 9 32
- L Caudate: -15 5 14
rTMS To The Dorsolateral Prefrontal Cortex. A Pilot Study

- Study Design: Treatment, Non-Randomized, Open Label, Single Group Assignment
- Subjects: Men and women between the ages of 18 and 60 years; Subjective, unilateral or bilateral, non-pulsatile tinnitus of 6 month's duration or greater; and Tinnitus Handicap Inventory score of 38 or greater
- Subjects will receive 20 active rTMS treatments applied to the left DLPFC over 4 consecutive weeks

ClinicalTrials.gov Identifier: NCT00886938
Patient Vignettes
Concluding Thoughts about rTMS for Tinnitus

- rTMS offers opportunity to affect focal cortical activity
  - Additional sites for stimulation
    - Auditory cortex
    - Dorsolateral Prefrontal Cortex
    - Parietal Association Center
    - Deeper Structures – Caudate, Striate nucleus, and Brain Stem

- Low-frequency (inhibitory) vs. high-frequency (excitatory)

- Number of pulses
Conclusion

- No cure for tinnitus
- Successful treatment involves
  - Reassurance; positive relationship with patient
  - Medication (alprazolam, amitriptyline, melatonin) for secondary consequences
  - Masking devices
  - Biofeedback – Tinnitus Retraining Therapy, cognitive-behavioral therapy
- Promising treatments
  - Neuromonics
  - rTMS
For Slide Presentation, visit: 
http://oto2.wustl.edu/clinepi/presentations.html

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Neuromonics Tinnitus Treatment
How the Neuromonics Tinnitus Treatment Addresses the Neurological Processes Underlying Clinically Significant Tinnitus

Auditory Stimulation to Address the Effects of Auditory Deprivation

- Achieved through the use of a wide-frequency stimulus that is spectrally modified to account for each patient’s hearing thresholds
- An objective of the treatment is to stimulate the integrative pathways of the auditory system
Relaxation and Relief to Address the Aversive Reaction / Stress Response

- Key objective is to reduce the engagement of the limbic system/amygdala and autonomic nervous system, which are major contributors to tinnitus-related disturbance
- This objective is addressed through the use of relaxing music as part of the acoustic stimulus as well as through the facilitation of a sense of relief from the tinnitus perception
- These effects are reinforced and complemented by treatment-facilitated improvements in sleep, as well as by benefits arising from the broader counseling and support program
Systematic Desensitization to Address the Perceptual Filters That Lead to Attention to the Tinnitus

- Seeks to address the attentional processes underlying the condition using a novel application of the principles of systematic desensitization.
- A common behavior therapy technique, systematic desensitization uses a graduated exposure to increasing hierarchies of anxiety-provoking situations while a person is in a state of deep relaxation, which facilitates desensitization to the anxiety-provoking stimulus.
- In applying these principles to the treatment of tinnitus, relaxing music was incorporated into the Neuromonics approach instead of the traditional progressive muscle relaxation training.
Hearing thresholds are measured using standard audiological procedures.

Spectral modification is then applied across the full frequency range up to 12.5 kHz.

Psychoacoustic measures are used to characterize the tinnitus as a basis for tinnitus education and counseling and for monitoring of the patient’s progress through treatment.

Tinnitus pitch and loudness matching is performed.
rTMS
Repetitive Transcranial Magnetic Stimulation

- Novel diagnostic and therapeutic tool
- Coil placed on scalp that generates magnetic pulses of very short duration (100–300 μs) at approximately 1.5 - 2.0 Tesla in strength
- High-frequency (≥ 5 Hz) to induce long-term synaptic potentiation
- Low-frequency (≈ 1 Hz) to induce long-term synaptic depression
Observations from rTMS studies in Depression

Greater Efficacy seen with

- Higher intensity of stimulation (above motor threshold)
- Longer Duration of stimulation – (4, 6, and 8 weeks)
Recommendations from our Experience with rTMS

- Electrical stimulation studies should be combined with neuroimaging (PET, fMRI, fcMRI) studies
- Association of changes in neural activity/networks and clinical response
- Creates a temporary localized lesion in a circumspect area of the brain
- Can be used to test different excitatory and inhibitory circuits in the brain
- Temporary effects can be followed by more enduring changes in neuronal excitability with low frequency (1 hz) stimulation
### THI change

The GLM Procedure  
Least Squares Means

| Treatment | THI change LSMEAN | Standard Error | H0:LSMEAN=0 Pr>|t| | H0:LSMean1=LSMean2 t-Value Pr > |t| |
|-----------|-------------------|----------------|-----------------|-------------------|
| B         | -9.33333333       | 2.29068161     | 0.0022          | 0.05              | 0.9600          |
| C         | -9.50000000       | 2.29068161     | 0.0020          |                   |                 |
Neotonus Neopulse

- NeoPulse is unlike other stimulators that produce fields that are "flat" and spread out over the entire surface area of the magnet array.
- NeoPulse is "bell-shaped" providing stronger power at the focal point in the center of the magnet array and much less power at the periphery of the field.
- This magnetic field configuration permits more specific targeting of the area of the brain of interest rather than the application of the same intensity of stimulation to areas of the brain peripheral to the area of interest.