Dear Colleagues,

With more than 300 participants and almost 200 scientific contributions (oral presentations and posters) the 3rd Tinnitus Research Initiative Meeting became the biggest Tinnitus Event of the year. According to the motto “From Clinical Practice to basic Neuroscience and back” the meeting focused on translational research in both directions: from clinical practice to basic research and from basic science to clinical research. The Tinnitus Research Initiative is convinced that it is the close collaboration between clinicians from different disciplines and basic researchers working with different technologies, which may bring the solution for tinnitus. For sure we are aware of all the difficulties, but it is through these meetings that we can find a common language and learn to better understand each other. We are convinced, that interaction among researchers, both during scientific sessions and informal bar discussions, is the way to connect the different pieces of the puzzle named “tinnitus”. One - out of numerous - examples of such connections is related to neramexane, which is currently in Phase III and might become the first drug that will be approved for tinnitus treatment. Neramexane has been developed by a German Pharmaceutical Company. It acts on nicotinic cholinergic receptors in the inner ear, which have been discovered by Ana Belen Elgoyhen, a basic neuroscientist in Buenos Aires. A hypothesis for a role of these inhibitory receptors in tinnitus generation comes now from a computer model of the auditory pathways developed by Lucas Parra, a computational neuroscientist in New York. Thus, the interaction of these different researchers may provide a rationale towards understanding which forms of tinnitus may especially benefit from this new treatment and generate new ideas for other forms of treatments. This is the reason why TRI will continue to foster interactions between audiologists, neuroscientists, otologists, psychologists, neurologists, hearing aid manufacturers, pharmacologists, and psychiatrists. Organized together with the University of Texas at Dallas, the 4th International TRI Tinnitus Conference: Frontiers in Tinnitus Research will take place from June 9-11 in Dallas (see also page 2)

Berthold Langguth
Susanne Staudinger
Fourth International TRI Tinnitus Conference
Frontiers in Tinnitus Research
Organized by the Tinnitus Research Initiative and The University of Texas at Dallas

When: June 9 - 11, 2010
Where: The Adolphus, 1321 Commerce Street, Dallas, Texas 75202, USA

For more information please look at http://www.tinnitusresearch.org

Please mark your calendars for this most important tinnitus event of the year!
Upcoming Meetings

3rd International Conference on Auditory Cortex
When: August 29 – September 02, 2009
Where: Herrenkrug Parkhotel, Magdeburg, Germany
Contact: Conventus Congressmanagement & Marketing GmbH
Markt 8
07743 Jena
Phone: 0049 (0)3641 3 53 32 25
E-Mail: ac2009@conventus.de
Detailed information: http://www.auditory-cortex.de/

27th Politzer Society Meeting
When: September 3 – 5, 2009
Where: The Queen Elisabeth II Conference Centre, London, UK
Sterling Events Ltd, 62 Hope Street
Liverpool L1 9BZ UK
Phone: 0044 (0)151 709 8979
Fax: 0044 (0)151 708 9861
Detailed information: http://www.politzerlondon.com

9th International Conference on Theoretical and Computational Acoustics 2009
When: September 7 – 11, 2009
Where: Dresden, Germany
Contact: Dr. Steffen Marburg
c/o Inst. für Festkörpermechanik
Technische Universität Dresden
01062 Dresden
Germany
Phone: 0049 351 4633 7976
Fax: 0049 351 4633 7969
E-Mail: info@ictca2009.com
Detailed information: http://www.ictca2009.com

Medical Physics and Biomedical Engineering World Congress 2009
When: September 7 – 12, 2009
Where: ICM, International Congress Center Munich, Germany
Contact: VDE CONFERENCE SERVICES
Stresemannallee 15
60596 Frankfurt am Main
Germany
Phone: 0049 (0)69 - 63 08-229/ -477
Fax: 0049 (0)69 - 96 31- 52 13
E-Mail: wc2009@vde.com
Tinnitus Discovery - Asia & Pacific Tinnitus Symposium
When: September 11 – 12, 2009
Where: Auckland Maritime Museum, New Zealand
E-Mail: tinnitus@auckland.ac.nz

17th Annual Conference on Management of the Tinnitus Patient
When: September 24 – 26, 2009
Where: Pomerantz Family Pavilion, Iowa City, USA
Contact: The University of Iowa
250 CEF
Iowa City, IA, 52242-5000
Phone: 001 800-551-9029
Fax: 001 319-335-4039

International Hearing Society (IHS) – 57th Annual Convention and Expo
When: September 24 – 28, 2008
Where: Savannah, Georgia, USA
Phone: +1 (0) 734-522-7200
Detailed information: http://ihsinfo.org/IhsV2/Conv2008/Index.cfm

Future Leaders of Audiology Conference (FLAC) 2009
When: October 1 – 3, 2009
Where: Reston, VA, USA
Contact: American Academy of Audiology
Attn: FLAC 2009
11730 Plaza America Drive, Suite 300
Reston, VA 20190
Phone: 001 800-222-2336 (Ed Sullivan) or
Fax: 001 319-335-4039, ext. 1051 (Sarah Sebastian)
Detailed information: http://www.audiology.org

2009 International Tinnitus Forum
When: October 3, 2009
Where: San Diego, CA, USA
Contact: Barbara Goldstein, PhD, CCC
Phone: 001 718-773-8888
E-Mail: metrc@inch.com
Detailed information: http://www.entnet.org/Community/named_minis_tinnitus.cfm

113th American Academy of Otolaryngology, Head and Neck Surgery Annual Meeting
When: October 4 – 7, 2009
Where: San Diego, CA, USA
Detailed information: http://www.entnet.org/annual_meeting/index.cfm
10th Anniversary Leicester Balance Course
When: October 13 - 15, 2009
Where: Leicester Tigers Rugby Stadium, Leicester, UK
Phone: 0044 (0)845 226622
E-Mail: emma@biosensemedical.com

The 7th Meeting of the British Society of Neuro-Otology
When: October, 16, 2009
Where: Leicester Tigers Rugby Stadium, Leicester, UK
Contact: Miss J Mills
Neuro-Otology Group
Imperial College London, Charing Cross Hospital
Fulham Palace Road London W6 8RF
Phone: 0044 (0)208 846 7285
Fax: 0044 (0)208 846 7577
E-Mail: neuro-otology@imperial.ac.uk
Detailed information: http://www.bsno.org.uk/Oct16-09-meeting.html

54th International Congress of Hearing Aid Acousticians
When: October 21 – 23, 2009
Where: Congress Center Nürnberg, CCN East, Germany
Detailed information: http://www.euha.org

Herbsttagung Arbeitsgemeinschaft Deutschsprachiger Audiologen und Neurootologen (ADANO)
When: October, 22 - 24, 2009
Where: Rhein-Mosel-Halle, Koblenz, Germany
Contact: Karin Scharbach
Katholisches Klinikum Koblenz
Rudolf-Virchow-Str. 7
56073 Koblenz
Phone: 0049 (0) 261 4 96-31 11
Fax: 0049 (0) 261 4 96-31 19
E-Mail: hno-adano@kk-koblenz.de
Detailed information: http://www.hno.org/adano/Adano_2009_Herbsttagung.pdf

158th Meeting of the Acoustical Society of America
When: October 26 – 30, 2009
Where: San Antonio, Texas, USA
E-Mail: asa@aip.org
Detailed information: http://www.asa.aip.org/meetings.html
The Ear Foundation – Cochlear implants 2008: The State of the Art
When:   November 7, 2009
Where:   National College for School Leadership , Nottingham, United Kingdom
Detailed Information:  http://www.earfoundation.org.uk

ASHA Convention 2009 - American Speach-Hearing-Language Association
When:   November 19 - 21, 2009
Where:   New Orleans, Lousiana, USA
Detailed Information:  http://www.asha.org/about/events/convention

The 7th Asia Pacific Symposium on Cochlear Implants and related Sciences (APSCI)
When:   December 1 – 4, 2009
Where:   Raffles City Convention Center, Singapore
Contact:  APSCI 2009 Symposium Manager
          73 Bukit Timah Road
          Rex House, #03-01
Phone:   0065 6330 6730
Fax:   0065 6336 2123
E-Mail:  apsci2009@pwevent.com

33rd MidWinter Meeting of the Association for Research in Otolaryngology (ARO)
When:   February 6 – 10, 2010
Where:   The Disneyland Hotel Anaheim, California, USA
Contact:  Alex Springer
E-Mail:  aspringer@talley.com
Detailed Information:  http://www.aro.org/mwm/mwm.html

American Auditory Society, Annual Meeting
When:   March 4 – 6, 2010
Where:   Scottsdale, AZ, USA
Contact:  American Auditory Society
Detailed Information:  http://www.amausitorysoc.org/annual-meeting/reginfo.htm
DAGA 2010: 36. Jahrestagung der Deutschen Gesellschaft für Akustik DEGA
When: March 15 – 18, 2010
Where: Berlin, Germany
Contact: Dipl.-Ing. Judith Kokavecz
Technische Universität Berlin
Institut für Strömungsmechanik und Technische Akustik
Einsteinufer 25
10587 Berlin
E-Mail: info2010@daga-tagung.de
Detailed Information: http://www.daga-tagung.de/2010

13. Jahrestagung der Deutschen Gesellschaft für Audiologie (DGA e.V.)
When: March 17 – 20, 2010
Where: Frankfurt, Germany
Contact: Deutsche Gesellschaft für Audiologie e.V.
Geschäftsstelle
c/o Haus des Hörens
Marie-Curie-Straße 2
26129 Oldenburg (Germany)
Phone: 0049 04 41 2172 500
Fax: 0049 04 41 2172 550
E-Mail: info@dga-ev.com

AudiologyNOW! 2010
When: April 14 – 17, 2010
Where: San Diego Convention Center, CA, USA
Detailed Information: http://www.audiologynow.org

159th Meeting of the Acoustical Society of America (ASA)
When: April 19 – 23, 2010
Where: Miami, Florida, USA
Detailed Information: http://asa.aip.org/meetings.html

81. Jahresversammlung der Deutschen Gesellschaft für Hals-Nasen-Ohren-Heilkunde, Kopf- und Hals-Chirurgie e.V.
When: May 12 – 16, 2010
Where: Rhein-Main-Hallen, Wiesbaden, Germany
Contact: Deutsche Gesellschaft für Hals-Nasen-Ohren-Heilkunde,
Kopf- und Hals-Chirurgie
Hittorfstr. 7
53129 Bonn (Germany)
Phone: 0049 (0)2 28/23 17 70
Fax: 0049 (0)2 28/23 17 70
E-Mail: info@hno.org
Detailed Information: http://www.hno.org/veranstaltungen/ankuendigungen.html
ESPO 2010 European Society of Pediatric Otorhinolaryngology
When: June 05 – 08, 2010
Where: Baluarte Conference Centre, Pamplona, Spain
Contact: Secretaría Científica
ORL Congresos, S.L.
C/ Fundadores, nº 13
28028 Madrid, Spain
Phone: 0034 91 575 93 93
Fax: 0034 91 431 26 92
E-Mail: orlcongresos@seorl.net
Detailed Information: http://www.espopamplona2010.com/

Human Brain Mapping Annual Meeting
When: June 06 – 10, 2010
Where: Barcelona, Spain
Detailed Information: www.humanbrainmapping.org

4th International TRI Tinnitus Conference. Frontiers in Tinnitus Research
When: June 09 – 11, 2010
Where: The Adolphus Hotel, Dallas, Texas, USA
E-Mail: dallas2010@tinnitusresearch.org
Detailed Information: http://www.tinnitusresearch.org/

4th World Congress of International Federation of Head and Neck Oncologic Societies (IFHNOS)
When: June 15 – 19, 2010
Where: Lotte Hotel, Seoul, Korea
Contact: IFHNOS 2010 Congress Secretariat
c/o Meci International Convention Services, Inc.
Rm. 1906, 19th floor Daerung Post Tower #1 212-8 Guro-dong, Guro-gu Seoul 152-790
Phone: 0082-2-2082-2310
Fax: 0082-2-2082-2314
E-Mail: ifhnos2010@ifhnos2010.org
Detailed Information: http://www.ifhnos2010.org/

CI2010 - 11th International Conference on Cochlear Implants and other Implantable Auditory Technologies
When: June 30 – July 03, 2010
Where: Stockholm International Fairs (Stockholmsmässan), Stockholm, Sweden
Contact: MCI Stockholm
Box 6911
102 39 Stockholm, Sweden
Phone: 0046 8 5465 1500
Fax: 0046 8 5465 1599
E-Mail: ci2010@mci-group.com
Detailed Information: http://www.ci2010.com
I Epidemiology

**Occupational noise-induced tinnitus: does it affect workers’ quality of life?**


Muluk NB, Oguztürk O.

ENT Department, Faculty of Medicine, Kirikkale University, Kirikkale, Turkey. nbayarmuluk@yahoo.com

OBJECTIVES: This prospective study aimed to investigate the quality of life of workers in a steel factory.

METHODS: The study group was composed of 16 male workers with tinnitus and 30 ears. Fifteen male workers without tinnitus and 30 ears were included into the control group. Workers were evaluated by questionnaire, pure-tone audiometry, and the SF-36 Health Survey. In the study group, tinnitus loudness levels (TLLs) were found. RESULTS: In the study group, the domains general mental health and role limitations owing to emotional problems were significantly lower than in the control group. Older age, industrial noise exposure over a long period, higher noise exposure during work, and hearing loss secondary to occupational noise caused workers to experience higher TLLs. Earheadings protected workers more than earplugs, and TLLs were lower. Important factors that affect workers’ quality of life are maximum exposed noise levels, daily and total noise exposure time, and exposure to continuous noise. Occupational noise-induced tinnitus mainly causes emotional disability rather than physical disability. Emotionally impaired QOL results may be due to tinnitus-related psychological problems.

CONCLUSION: Workers should have knowledge about the hazardous effects of noise. Periodic health checkups and regular seminars have great importance. Workers must be aware of other ototoxic factors, such as medications and noisy music. In the future, researchers should develop a screening method to detect those with a more hereditary affinity to hearing loss.

**Intentional Exposure to Loud Music: The Second MTV.com Survey Reveals an Opportunity to Educate.**


de Lourdes Quintanilla-Dieck M, Artunduaga MA, Eavey RD.

Pediatric Otolaryngology Service, Department of Otolaryngology, Massachusetts Eye and Ear Infirmary, Department of Otology and Laryngology, Harvard Medical School (M.Q., M.A., R.E.), Boston, MA, and the Vanderbilt Bill Wilkerson Center for Otolaryngology and Communication Sciences, Departments of Otolaryngology and Hearing & Speech Sciences, Vanderbilt University School of Medicine (R.E.), Nashville, TN.

OBJECTIVES: Music-induced hearing loss (MIHL), an unconsciously self-inflicted public health concern, could evolve into an epidemic because of the appeal of loud music. After media attention about a previous hearing-loss survey with Music Television (MTV.com), we hypothesized that a repeat survey could compare awareness and behavior trends. STUDY DESIGN: We incorporated the 2002 survey into the new 73-question instrument presented to random visitors on the MTV.com website in 2007. A P < .05 value was used for independent t and z-tests. RESULTS: A total of 2500 completed surveys were analyzed. Hearing loss was considered a problem by 32% of respondents compared with other health issues such as drug/alcohol use (62%). However, nearly half of the respondents admitted experiencing symptoms such as tinnitus or hearing loss after loud music exposure. Health care providers were the least likely source of MIHL awareness despite the respondents favoring provider education for hearing protection behavior modification. CONCLUSION: Most respondents still could not recall learning about prevention of potential hearing loss, although the media has become the most informative source. Most respondents indicated that they would adopt protective ear behavior if made aware of hearing loss risk, especially if informed by health care professionals, revealing an educational opportunity.
Tinnitus distress, anxiety, depression, and hearing problems among cochlear implant patients with tinnitus.

Andersson G, Freijd A, Baguley DM, Idrizbegovic E.

Swedish Institute for Disability Research, Department of Behavioural Sciences and Learning, Linköping University, Linköping, Sweden. Gerhard.Andersson@liu.se

BACKGROUND: While several studies have investigated the presence and annoyance of tinnitus in cochlear implant (CI) recipients, few studies have probed the handicap experienced in association with tinnitus in this population.

PURPOSE: The aim of this study was to use validated self-report measures in a consecutive sample of CI patients who reported tinnitus in order to determine the extent of tinnitus handicap.

RESEARCH DESIGN: In a retrospective design, a total of 151 patients (80% response rate) responded to a postal questionnaire, and of these, 111 (74%) reported that they currently experienced tinnitus and were asked to complete the full questionnaire. Sampling was performed at a point of a mean 2.9 years postsurgery (SD = 1.8 years). Three established self-report questionnaires were included measuring tinnitus handicap (Tinnitus Handicap Inventory [THI]), hearing problems (Gothenburg Profile), and finally, a measure of anxiety and depression (Hospital Anxiety and Depression Scale).

We analyzed the data by means of Pearson product moment correlations, t-tests, ANOVAs, and chi-square.

RESULTS: Data from the validated questionnaires showed relatively low levels of tinnitus distress, moderate levels of hearing problems, and low scores on the anxiety and depression scales. Using the criteria proposed for the THI (which was completed by 107 patients), 35% (N = 38) had a score indicating "no handicap," 30% (N = 32) "mild handicap" 18% (N = 19) "moderate handicap", and 17% (N = 18) "severe handicap." Thus 37 individuals from the total series of 151 reported moderate to severe tinnitus handicap (24.5%). Tinnitus distress was associated with increased hearing problems, anxiety, and depression.

CONCLUSION: Tinnitus can be a significant problem following CI, but that the experienced distress is often moderate. However, a quarter of CI recipients do demonstrate moderate/severe tinnitus handicap, and thus are candidates for tinnitus specific therapy. The level of tinnitus handicap is associated with hearing problems and psychological distress.

Association between hearing loss level and degree of discomfort introduced by tinnitus in workers exposed to noise.

Dias A, Cordeiro R.

Faculdade de Medicina de Botucatu, UNESP.

Hearing loss and tinnitus impact the lives of workers in every instance of their lives. AIM: This paper aims to investigate the existence of a dose-response relationship between hearing loss and tinnitus by determining whether higher levels of hearing loss can be associated with increased tinnitus-related discomfort.

MATERIALS AND METHOD: This cross-sectional case study assessed 284 workers exposed to occupational noise through pure tone audiometry. Test results were categorized as defined by Merluzzi. Individuals complaining of tinnitus answered the adapted and validated Brazilian Portuguese version of the Tinnitus Handicap Inventory. A generalized linear model was adjusted for binomial data to test the interaction between these factors.

RESULTS: Over 60% of the ears analyzed had hearing loss, while more than 46% of them had tinnitus. Tinnitus prevalence and risk rates increased as pure tone audiometry results got worse. The association between both, considering all hearing loss degrees, was statistically significant.

CONCLUSION: The results point to a statistical association between hearing loss and tinnitus; the greater the hearing loss, the greater the discomfort introduced by tinnitus.
Characterization of tinnitus in the elderly and its possible related disorders.

Ferreira LM, Ramos Júnior AN, Mendes EP.
Departamento de Saúde Comunitária, Faculdade de Medicina, Universidade Federal do Ceará.

Population aging it is a current reality in Brazil and tinnitus appears as a very prevalent symptom, having a high impact on the quality of life of elderly patients. AIM: To evaluate and to characterize tinnitus in this group. MATERIALS AND METHODS: A research questionnaire randomly given to 100 elderly patients in a tertiary hospital, asking about tinnitus characteristics, its impact on the life of the patient, and personal medical history. RESULTS: 61% of the participants were female, average age average was 69.53 years. The results associated with tinnitus features were: no-pulsatile 76%, continuous 54%, bilateral 57%, recent 62% and alone 83%;32.5% had emotional disorders, 31.8% had sleep disorders, 22.5% had difficulties concentration and 13.2% had social problems; 39% classified their tinnitus in moderate; 35% had intense tinnitus and 26% considered it a mild one: as to comorbidities: relation with neurotology symptoms and hypertension; as for associations with audiometry findings: descending, sensorineural and symmetrical curves prevailed. CONCLUSIONS: Tinnitus has a relevant impact on the lives of the elderly; there was no correlation between the level of hearing loss and the level of patient dissatisfaction caused by tinnitus; and presbycusis was the most common finding in the audiometric tests.

Prevalence of depression and antidepressant use in an otolaryngology patient population.

Chandra RK, Epstein VA, Fishman AJ.
Department of Otolaryngology-Head and Neck Surgery, Feinberg School of Medicine, Northwestern University, Chicago, IL.

OBJECTIVE: To determine the prevalence of depressive diagnoses and antidepressant use in various subsets of otolaryngology patients. STUDY DESIGN: Academic practice EMR database query. SUBJECTS AND METHODS: Over 12,000 consecutive otolaryngology patients were analyzed by primary diagnosis and in three groups: Group 1 (tinnitus, vertigo), Group 2 (rhinosinusitis), and Group 3 (sleep apnea). The number with depressive diagnoses and/or those taking antidepressants was determined. RESULTS: The prevalence of any depressive diagnosis was 11 percent, and 18 percent had been prescribed antidepressants. The prevalence of depression was 13 percent, 10 percent, and 14 percent for Groups 1, 2, and 3, respectively. Antidepressants had been prescribed in 21 percent, 15 percent, and 28 percent, respectively. The primary-encounter diagnosis with the highest incidence of depression (21%) and antidepressant use (46%) was sleep apnea with insomnia. CONCLUSION: Otolaryngology patients may exhibit greater prevalence of depression than is observed in the general population (7.3%). Highest prevalence was found in patients with inner ear disease and sleep apnea. Depression may be a cause of significant comorbidity in patients with chronic otolaryngic conditions.

The characteristics of tinnitus in workers exposed to noise.

Steinmetz LG, Zeigelboim BS, Lacerda AB, Morata TC, Marques JM.
Programa de Mestrado e Doutorado em Distúrbios da Comunicação, Universidade Tuiuti do Paraná.

Tinnitus is a common auditory complaint among individuals exposed to noise. AIM: this paper aims to study the characteristics of tinnitus in workers exposed to noise. STUDY DESIGN: this is a descriptive prospective study. MATERIALS AND METHOD: Fifty-two individuals averaging 29 years of age were enrolled in a hearing loss prevention program at a meat processing plant. The participants were interviewed and had their hearing tested in 2005 and 2006. RESULTS: seventy-one percent of the participants were found to have normal hearing. Tinnitus was present in 16% of the males and in 9% of the females. Mean noise exposure length was 7 years and noise levels ranged from 86 to 91 dBA (48%). Bilateral tinnitus (46%) of the hissing type (40%) and moderate intensity (49%) was the most prevalent. Symptoms began to be observed within one to five years after initial exposure to noise (67%).
and manifested themselves in weekly episodes (41%) that bothered the patients mostly at night (34%). A significant correlation was observed between the frequency of tinnitus episodes and the noise levels to which workers were exposed. **CONCLUSION:** tinnitus should be included in hearing loss prevention programs in order to more comprehensively promote occupational hearing health.

**Subjective tinnitus and hearing problems in adolescents.**

**Bulbul SF, Muluk NB, Cakir EP, Tufan E.**
Kirikkale University, Faculty of Medicine, Pediatry Department, Turkey.

**OBJECTIVES:** We investigated the hearing problems and tinnitus frequencies in adolescents at three public primary and two high schools. **METHODS:** This study was carried out at three public primary and two high schools. 428 Turkish school children (244 girls, 184 boys) were asked to voluntarily answer a set of questionnaires in their classrooms at the beginning of the training program. There were 250 students (105 male, 145 female) in Primary School and 178 (79 male, 99 female) students in High School. We used questionnaire to evaluate subjective tinnitus and hearing problems. Walkman usage, listening loud and noisy music, intra-familial physical trauma, concentration difficulty in class and school success were also evaluated. **RESULTS:** In age-related groups (Group 1=11-13 years; Group 2=13-15 years; Group 3=16-18 years), hearing loss was present in 32.1% of Group 1, 19% of Group 2 and 28.3% of Group 3. Listening loud and noisy music was reported in 81.8% of Group 1, 95.4% of Group 2 and 87% of Group 3. Tinnitus was present 36.8% in Group 2, 33.5% in Group 1 and 31.5% in Group 3. Tinnitus after listening loud music was present in 42.7% of Group 2, 36.1% of Group 3 and 25.6% of Group 1. Among all students with tinnitus, 19.5% considered their school success as very good, 41.1% as good and 39.4% as bad. In students, using Walkman, tinnitus was seen both in the right and left ears. **CONCLUSION:** Tinnitus may be seen in adolescents at primary and high schools. Listening loud and noisy music and Walkman usage may cause an increase in the frequency of tinnitus manifestation. Adolescents should be educed about the hazardous effects of loud music. Education should include families, teachers, students, and whole community. These issues should be taken into public health policy of the countries.

**Noise-induced hearing loss in children: A ‘less than silent’ environmental danger.**

**Harrison RV.**
Division of Neuroscience and Mental Health, The Hospital for Sick Children; Department of Otolaryngology - Head and Neck Surgery; Department of Physiology, University of Toronto, Toronto, Ontario.

A review of the problems of noise-induced hearing loss in children, especially related to recreational music and the use of personal entertainment devices. The pathophysiology of noise-induced hearing loss and its associated problems (eg, tinnitus) are discussed. The evidence for an increase in noise-induced hearing loss in children and young people is reviewed. Some practical advice (for clinicians, caregivers and children) on hearing loss prevention is provided.

**Too late smart: farmers’ adoption of self-protective behaviors in response to exposure to hazardous noise.**

**McCullagh M, Robertson C.**
Department of Nursing, North Dakota State University, Fargo, ND, USA.

Farmers are exposed to hazardous noise from equipment and livestock and experience high rates of noise-induced hearing loss (NIHL); however, their use of hearing protection devices (HPDs) is low. The purpose of this study was to describe farmers’ personal experiences using HPDs, influencing others’ use of HPDs, and overcoming barriers to the use of HPDs. A purposive sample of farmers who reported a high frequency of HPD use was selected for face-to-face interviews. Findings indicated that farmers have frequent exposure to hazardous noise. They described their motivation to adopt protective behaviors to
avoid hearing loss, noise annoyance, or tinnitus. Many tried to influence others’ use of HPD, particularly family members. These farmers have developed a variety of methods to ensure convenient access to HPDs when needed, and have developed effective techniques for overcoming common barriers to protection. Findings from this study will be used to form the foundation for future studies aimed at developing and testing an intervention to increase HPD use and decrease rates of NIHL among farmers.

II Pathophysiology

**Paradoxical long-term enhancement of distortion product otoacoustic emission amplitude after repeated exposure to moderate level, wide band noise in awake guinea pigs.**


Mei L, Huang ZW, Tao ZZ.  
Department of Otolaryngology-Head and Neck Surgery, Renmin Hospital, Wuhan University, China.  
Objective: Hearing sensitivity usually diminishes with noise exposure. In the present study, we examined the effect of 93 dB(A) wide band noise on cochlear micromechanical sensitivity in awake guinea pigs.  
Methods: Animals were randomly assigned to groups receiving either single or repeated noise exposure. Distortion product otoacoustic emission amplitudes were recorded before, during and after noise exposure.  
Results: Ninety-three decibel(A) wide band noise reduced the distortion product otoacoustic emission amplitudes at all tested frequencies. The distortion product otoacoustic emission amplitudes for higher frequencies showed a permanent reduction, whereas those for lower frequencies showed a temporary reduction. Distortion product otoacoustic emission amplitudes for middle frequencies showed prolonged enhancement after repeated noise exposure.  
Conclusion: Our results suggest that (1) it is likely that there are intermediate stages between permanent threshold shift and temporary threshold shift, and (2) long-term enhancement of distortion product otoacoustic emission amplitudes may be an indication of tinnitus generation.

**Salicylate, an aspirin metabolite, specifically inhibits the current mediated by glycine receptors containing alpha1-subunits.**

Br J Pharmacol. 2009 Jul 7. [Epub ahead of print]

Hefei National Laboratory for Physical Sciences at Microscale and School of Life Sciences, University of Science and Technology of China, Hefei, China.  
Background and purpose: Aspirin or its metabolite sodium salicylate is widely prescribed and has many side effects. Previous studies suggest that targeting neuronal receptors/ion channels is one of the pathways by which salicylate causes side effects in the nervous system. The present study aimed to investigate the functional action of salicylate on glycine receptors at a molecular level.  
Experimental approach: Whole-cell patch-clamp and site-directed mutagenesis were deployed to examine the effects of salicylate on the currents mediated by native glycine receptors in cultured neurones of rat inferior colliculus and by glycine receptors expressed in HEK293T cells.  
Key results: Salicylate effectively inhibited the maximal current mediated by native glycine receptors without altering the EC(50) and the Hill coefficient, demonstrating a non-competitive action of salicylate. Only when applied simultaneously with glycine and extracellularly, could salicylate produce this antagonism. In HEK293T cells transfected with either alpha1-, alpha2-, alpha3-, alpha1beta-, alpha2beta- or alpha3beta-glycine receptors, salicylate only inhibited the current mediated by those receptors that contained the alpha1-subunit. A single site mutation of I240V in the alpha1-subunit abolished inhibition by salicylate.  
Conclusions and implications: Salicylate is a non-competitive antagonist specifically on glycine receptors containing alpha1-subunits. This action critically involves the isoleucine-240 in the first transmembrane segment of the alpha1-subunit. Our findings may increase our understanding of the receptors involved in the side effects of salicylate on the central nervous system, such as seizures and tinnitus.
Neurofibromatosis type 2 (NF2): a clinical and molecular review.
Orphanet J Rare Dis. 2009 Jun 19;4:16.

Evans DG.
Medical Genetics Research Group, Regional Genetics Service and National Molecular Genetics
Reference Laboratory, Central Manchester Foundation Trust, St Mary's Hospital, Manchester M130JH,
UK. dgr.evans@virgin.net

Neurofibromatosis type 2 (NF2) is a tumour-prone disorder characterised by the development of
multiple schwannomas and meningiomas. Prevalence (initially estimated at 1: 200,000) is around 1 in
60,000. Affected individuals inevitably develop schwannomas, typically affecting both vestibular nerves
and leading to hearing loss and deafness. The majority of patients present with hearing loss, which is
usually unilateral at onset and may be accompanied or preceded by tinnitus. Vestibular schwannomas
may also cause dizziness or imbalance as a first symptom. Nausea, vomiting or true vertigo are rare
symptoms, except in late-stage disease. The other main tumours are schwannomas of the other cranial,
spinal and peripheral nerves; meningiomas both intracranial (including optic nerve meningiomas) and
intraspinal, and some low-grade central nervous system malignancies (ependymomas). Ophthalmic
features are also prominent and include reduced visual acuity and cataract. About 70% of NF2 patients
have skin tumours (intracutaneous plaque-like lesions or more deep-seated subcutaneous nodular
tumours). Neurofibromatosis type 2 is a dominantly inherited tumour predisposition syndrome caused
by mutations in the NF2 gene on chromosome 22. More than 50% of patients represent new mutations
and as many as one-third are mosaic for the underlying disease-causing mutation. Although truncating
mutations (nonsense and frameshifts) are the most frequent germline event and cause the most severe
disease, single and multiple exon deletions are common. A strategy for detection of the latter is vital
for a sensitive analysis. Diagnosis is based on clinical and neuroimaging studies. Presymptomatic
genetic testing is an integral part of the management of NF2 families. Prenatal diagnosis and pre-
implantation genetic diagnosis is possible. The main differential diagnosis of NF2 is schwannomatosis.
NF2 represents a difficult management problem with most patients facing substantial morbidity and
reduced life expectancy. Surgery remains the focus of current management although watchful waiting
with careful surveillance and occasionally radiation treatment have a role. Prognosis is adversely
affected by early age at onset, a higher number of meningiomas and having a truncating mutation. In the
future, the development of tailored drug therapies aimed at the genetic level are likely to provide huge
improvements for this devastating condition.

The nicotinic receptor of cochlear hair cells: A possible pharmacotherapeutic target?
Biochem Pharmacol. 2009 May 27. [Epub ahead of print]

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Mechanosensory hair cells of the organ of Corti transmit information regarding sound to the central
nervous system by way of peripheral afferent neurons. In return, the central nervous system provides
feedback and modulates the afferent stream of information through efferent neurons. The medial
olivocochlear efferent system makes direct synaptic contacts with outer hair cells and inhibits
amplification brought about by the active mechanical process inherent to these cells. This feedback
system offers the potential to improve the detection of signals in background noise, to selectively
attend to particular signals, and to protect the periphery from damage caused by overly loud sounds.
Acetylcholine released at the synapse between efferent terminals and outer hair cells activates a peculiar
nicotinic cholinergic receptor subtype, the alpha9alpha10 receptor. At present no pharmacotherapeutic
approaches have been designed that target this cholinergic receptor to treat pathologies of the auditory
system. The potential use of alpha9alpha10 selective drugs in conditions such as noise-induced hearing
loss, tinnitus and auditory processing disorders is discussed.
Central auditory plasticity after carboplatin-induced unilateral inner ear damage in the chinchilla: Up-regulation of GAP-43 in the ventral cochlear nucleus.

Hear Res. 2009 May 10.

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Inner ear damage may lead to structural changes in the central auditory system. In rat and chinchilla, cochlear ablation and noise trauma result in fiber growth and synaptogenesis in the ventral cochlear nucleus (VCN). In this study, we documented the relationship between carboplatin-induced hair cell degeneration and VCN plasticity in the chinchilla. Unilateral application of carboplatin (5mg/ml) on the round window membrane resulted in massive hair cell loss. Outer hair cell degeneration showed a pronounced basal-to-apical gradient while inner hair cell loss was more equally distributed throughout the cochlea. Expression of the growth associated protein GAP-43, a well-established marker for synaptic plasticity, was up-regulated in the ipsilateral VCN at 15 and 31 days post-carboplatin, but not at 3 and 7 days. In contrast, the dorsal cochlear nucleus showed only little change. In VCN, the high-frequency area dorsally showed slightly yet significantly stronger GAP-43 up-regulation than the low-frequency area ventrally, possibly reflecting the high-to-low frequency gradient of hair cell degeneration. Synaptic modification or formation of new synapses may be a homeostatic process to re-adjust mismatched inputs from two ears. Alternatively, massive fiber growth may represent a deleterious process causing central hyperactivity that leads to loudness recruitment or tinnitus.

Predicting tinnitus pitch from patients' audiograms with a computational model for the development of neuronal hyperactivity.

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Tinnitus is often related to hearing loss, but how hearing loss could lead to tinnitus has remained unclear. Animal studies show that the occurrence of tinnitus is correlated to increased spontaneous firing rates of central auditory neurons, but mechanisms that give rise to such hyperactivity have not been identified yet. Here we present a computational model that reproduces tinnitus-related hyperactivity and predicts tinnitus pitch from the audiograms of tinnitus patients with noise-induced hearing loss and tone-like tinnitus. Our key assumption is that the mean firing rates of central auditory neurons are controlled by homeostatic plasticity. Decreased auditory nerve activity after hearing loss is counteracted through an increase of the neuronal response gain, which restores the mean rate but can also lead to hyperactivity. Hyperactivity patterns calculated from patients' audiograms exhibit distinct peaks at frequencies close to the perceived tinnitus pitch, corroborating hyperactivity through homeostatic plasticity as a mechanism for the development of tinnitus after hearing loss. The model suggests that such hyperactivity, and thus also tinnitus caused by cochlear damage, could be alleviated through additional stimulation.

[Functional and activity-dependent plasticity mechanisms in the adult and developing auditory brain]
[Article in Spanish]

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INTRODUCTION AND DEVELOPMENT: Sensory systems show a topographic representation of the sensory epithelium in the central nervous system. In the auditory system this representation originates tonotopic maps. For the last four decades these changes in tonotopic maps have been widely studied either after peripheral mechanical lesions or by exposing animals to an augmented acoustic
environment. These sensory manipulations induce plastic reorganizations in the tonotopic map of the auditory cortex. By contrast, acoustic trauma does not seem to induce functional plasticity at subcortical nuclei. Mechanisms that generate these changes differ in their molecular basis and temporal course and we can distinguish two different mechanisms: those involving an active reorganization process, and those that show a simple reflection of the loss of peripheral afferences. Only the former involve a genuine process of plastic reorganization. Neuronal plasticity is critical for the normal development and function of the adult auditory system, as well as for the rehabilitation needed after the implantation of auditory prostheses. However, development of plasticity can also generate abnormal sensation-like tinnitus. Recently, a new concept in neurobiology so-called 'neuronal stability' has emerged and its implications and conceptual basis could help to improve the treatments of hearing loss. CONCLUSION: A combination of neuronal plasticity and stability is suggested as a powerful and promising future strategy in the design of new treatments of hearing loss.

Spiral ganglion cell loss is unrelated to segmental cochlear sensory system degeneration in humans.
Otol Neurotol. 2009 Apr;30(3):418-422.

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OBJECTIVE: To demonstrate that contrary to what occurs in animals, neuron loss in the human spiral ganglion is not in proportion to organ of Corti hair or supporting cell loss. STUDY DESIGN: Histopathological review of archival temporal bone histological sections. SETTING: Nonprofit research facility. METHODS: Four temporal bones, from an archival collection of 1,448 temporal bones, were found that had a total loss of hair and supporting cells limited to the basal segment of the cochlea and a hearing loss of 3 or more years (range, 3-28 yr). Cochlear reconstructions were conducted to demonstrate the populations of hair and supporting cells, peripheral processes (dendrites), spiral ganglion cells, and the amount of surviving stria vascularis in different cochlear segments. RESULTS: The total loss of hair and supporting cells of the organ of Corti in the base of the cochlea is not accompanied by a proportional loss of spiral ganglion cells in the modiolar base. CONCLUSION: A long-term loss of hearing in frequencies greater than 2 kHz, and corresponding hair cell loss, does not result in a subsequent loss of spiral ganglion cells in humans, in contrast to what has been reported in association with animals. These findings suggest that the poor performance of cochlear implant in patients after prolonged deafness is not caused by ongoing degeneration of ganglion cells.

III Diagnostics

Could an underlying hearing loss be a significant factor in the handicap caused by tinnitus?

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There have been several studies that have demonstrated a link between the hearing loss of subjects and tinnitus. However, there has been no systematic evaluation of the link between perceived tinnitus distress and an underlying hearing loss. The purpose of the current study is to explore this association, and ascertain whether a subject’s hearing loss contributes to the handicap caused by tinnitus. A group of 96 adults were evaluated with Pure Tone Audiometry and a questionnaire that included the Tinnitus Handicap Inventory (THI). In 58% of the subjects, the side of the unilateral or worse tinnitus corresponded with the ear with poorer hearing thresholds. A subset of the THI, the Two Question Mean (TQM) that was related to questions with regard to communication, correlated significantly with the hearing thresholds in the better hearing ear ( P < 0.01). There was also a significant correlation between the THI and TQM scores ( P < 0.01). These results suggested that in tinnitus subjects with impaired hearing, the underlying hearing loss may be a significant factor in the perceived distress.
DPOAE in estimation of the function of the cochlea in tinnitus patients with normal hearing.

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OBJECTIVE: The most probable place generating tinnitus in the auditory pathway is the outer hair cells (OHCs) inside the cochlea. Otoacoustic emissions are used to assess their activity. The objective of the investigation was to measure the features of distortion product otoacoustic emissions (DPOAE) in a group of tinnitus patients without hearing loss, estimate the diagnostic value of the parameters for the analysis of cochlear function in the patients, emphasizing those most useful in localizing tinnitus generators, and determine the hypothetical influence of hyperacusis and misophony on DPOAE parameters in tinnitus patients. PATIENTS AND METHODS: The material consisted of 44 patients with tinnitus and without hearing loss. In the control group were 33 patients without tinnitus with the same state of hearing. The tinnitus patients were divided into three subgroups: those with hyperacusis, those with misophonia, and those with neither. After collecting medical history and performing clinical examination of all the patients, tonal and impedance audiometry, ABR, and discomfort level were evaluated. Then DPOAE were measured using three procedures. First the amplitudes of two points per octave were assessed, second the "fine structure" method with 16-20 points per octave (f2/f1=1.22, L1=L2=70dB), and the third procedure included recording the growth function in three series for input tones of f2=2002, 4004, and 6006Hz (f2/f1=1.22) and L1=L2 levels increasing by increments of 5dB in each series. RESULTS AND CONCLUSIONS: Hyperacusis was found in 63% and misophonia in 10% of the tinnitus patients with no hearing loss. DPOAE amplitudes in recordings with two points per octave and the fine structure method are very valuable parameters for estimating cochlear function in tinnitus patients with normal hearing. Function growth rate cannot be the only parameter in measuring DPOAE in tinnitus patients, including subjects with hyperacusis and misophonia. The markedly higher DPOAE amplitudes in the group of tinnitus patients without hearing loss suggest that tinnitus may be caused by increased motility of the OHCs induced by decreasing efferent fiber activity, and not by OHC failure. Hyperacusis significantly increases the amplitude of DPOAE in tinnitus patients with no hearing loss.

Correlation analysis of the visual-analogue scale and the Tinnitus Handicap Inventory in tinnitus patients.
Braz J Otorhinolaryngol. 2009 Jan-Feb;75(1):76-79.

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One of the most challenging topics in tinnitus clinical studies is the measuring method used. Visual Analogue Scales (VAS) and Tinnitus Handicap Inventory (THI) are frequently used in tinnitus. AIM: To verify the relationship between VAS and THI scores in tinnitus patients in a prospective study. MATERIALS AND METHODS: 43 patients classified their tinnitus according to VAS and THI, and both scores were compared through the Spearman's correlation coefficient test. RESULTS: There was a correlation between the VAS and THI scores. CONCLUSION: There is correlation between VAS and THI scores in patients with sensorineural tinnitus.

Clinical and Carotid Ultrasonographic Features of Intracranial Dural Arteriovenous Fistulas in Patients with and without Pulsatile Tinnitus.
J Neuroimaging. 2009 May 18. [Epub ahead of print]

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ABSTRACT BACKGROUND AND PURPOSE Pulsatile tinnitus is a common symptom of intracranial dural arteriovenous fistulas (DAVF). This study aims to characterize the clinical and ultrasonographic features of DAVF in patients with pulsatile tinnitus. METHODS We compared the characteristics of DAVF
and carotid duplex sonography (CDS) results between 67 DAVF patients with and without pulsatile tinnitus. We also investigated the relationship between changes in tinnitus status and serial CDS changes in 25 DAVF patients with pulsatile tinnitus. RESULTS Pulsatile tinnitus was highly associated with the location and feeding arteries of DAVF (P < .001). The sensitivity of resistive index (RI; Norm, > .72) and end diastolic velocity (EDV; Norm, <21 cm/sec) of external carotid artery (ECA) in CDS study for diagnosing DAVF in patients with pulsatile tinnitus was 95% and 92%, respectively. Changes of RI and EDV of ECA also correlated with the changes of tinnitus status. CONCLUSIONS RI and EDV of ECA have high diagnostic sensitivity and reliability for detecting DAVF in patients with pulsatile tinnitus. J Neuroimaging 2009;XX:1-5.

The SF-36 Health Survey in tinnitus patients with a high jugular bulb.

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OBJECTIVES: This prospective study investigated the multi-item patient functions of health concepts using the SF-36 Health Survey in tinnitus patients with a high jugular bulb (HJB). METHODS: The study group consisted of 10 adult tinnitus patients (7 males, 3 females) with an HJB on temporal bone high-resolution computed tomography (HRCT). The control group consisted of 10 healthy patients with normal hearing levels (7 males and 3 females) without tinnitus. Using a questionnaire, a tinnitus loudness level score (TLL-Sc) was found. Using the SF-36 questionnaire, eight health concepts were evaluated: physical functioning (PF), role limitations due to physical problems (RP), social functioning (SF), bodily pain (BP), general mental health (MH), role limitations due to emotional problems (RE), vitality (VT), and general health perceptions (GH). RESULTS: SF and VT scores were significantly lower in the study group (p < .05). As the duration of the tinnitus increased, sleep problems and impaired SF-36 scores were seen. Higher TLL-Scs did not cause lower quality of life (QOL) scores, even though they are associated with significantly higher sleep disturbance. In males, TLL-Scs seem to be higher and SF-36 domains lower than in females. Older patients have lower TLL-Scs and do not have impaired HJB-related QOL results, although they do have sleep problems. CONCLUSION: Longer tinnitus duration, male gender, and sleeping problems may impair QOL. With higher TLL-Scs, QOL results are not lower owing to patients' getting used to living with their tinnitus. According to the SF-36 Health Survey, tinnitus patients appear to have a higher level of emotional disability than physical disability.

Tinnitus as a prognostic factor of sudden deafness.
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Conclusions. The ‘tinnitus-rare’ group had a poorer prognosis for hearing than the ‘tinnitus-often’ group in all sudden sensorineural hearing loss (SSNHL), although the ‘shorter duration’ group had better prognosis than the ‘longer duration’ when restricted to SSNHL accompanied by tinnitus. This indicates that tinnitus itself may not be a sign for poor hearing prognosis but might be an essential sound for the initiation of repair of a damaged auditory system. Objectives. We examined the hearing improvement rate (HIR) and tinnitus at the onset of SSNHL to elucidate the prognostic value of tinnitus accompanying SSNHL. Patients and methods. Fifty patients with SSNHL were treated with systemic administration of steroids. Hearing recovery was determined by comparing the hearing levels before and after treatment. Tinnitus was subjectively evaluated by the tinnitus scoring questionnaire. The score for the five-step evaluation of the subjective tinnitus feelings ‘loudness’, ‘duration’ and ‘annoyance’ was obtained at the onset. Results. In terms of ‘duration’, when we divided all the cases into ‘tinnitus-rare’ group and ‘tinnitus-often’ group, HIR in the ‘tinnitus-rare’ group was significantly lower than that in ‘tinnitus-often’ group. When restricted to the ‘tinnitus-often’ group, HIR for ‘shorter duration’ was significantly higher than that for ‘longer duration’.
Clinical presentation and management of jugular foramen paraganglioma.

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OBJECTIVES: Jugular foramen paraganglioma is a locally invasive, benign tumor, which grow slowly and causes various symptoms such as pulsatile tinnitus and low cranial nerve palsy. Complete surgical resection is regarded as the ideal management of these tumors. The goal of this study is to identify the clinical characteristics and most effective surgical approach for jugular foramen paraganglioma. METHODS: Retrospective analysis of 9 jugular foramen paraganglioma patients who underwent surgical resection between 1986 and 2005 was performed. Clinical records were reviewed for analysis of initial clinical symptoms and signs, audiological examinations, neurological deficits, radiological features, surgical approaches, extent of resection, treatment outcomes and complications. RESULTS: Most common initial symptom was hoarseness, followed by pulsatile tinnitus. Seven out of 9 patients had at least one low cranial nerve palsy. Seven patients were classified as Fisch Type C tumor and remaining 2 as Fisch Type D tumor on radiologic examination. Total of 11 operations took place in 9 patients. Total resection was achieved in 6 cases, when partial resection was done in 3 cases. Two patients with partial resection received gamma knife radiosurgery (GKS), when remaining 1 case received both GKS and two times of revision operation. No mortality was encountered and there were few postoperative complications. CONCLUSION: Neurologic examination of low cranial nerve palsy is crucial since most patients had at least one low cranial nerve palsy. All tumors were detected in advanced stage due to slow growing nature and lack of symptom. Angiography with embolization is crucial for successful tumor removal without massive bleeding. Infratemporal fossa approach can be considered as a safe, satisfactory approach for removal of jugular foramen paragangliomas. In tumors with intracranial extension, combined approach is recommended in that it provides better surgical view and can maintain the compliance of the patients.

Asymmetric hearing loss: rule 3,000 for screening vestibular schwannoma.

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OBJECTIVE: To assess the diagnostic yield of audiograms associated to electronystagmography (ENG) for screening vestibular schwannomas (VSs), to determine what definition of asymmetric sensorineural hearing loss (ASNHL) fits best for the diagnosis of VS, and to determine if cochleovestibular symptoms and atherosclerotic potential risk factors play a role in the VS screening. STUDY DESIGN: Retrospective chart review in a tertiary care center. METHODS: One hundred twenty-two patients were included in the study and divided into 2 groups: 1) patients presenting a VS (n = 74) and 2) patients without VS (n = 48). They had received an audiometry assessment, an ENG, and a posterior fossa magnetic resonance imaging (MRI). In addition, a variety of risk factors and clinical data were collected. Mean hearing threshold by frequency, mean asymmetries by frequency, speech discrimination score (SDS), ENG results, and presence or absence of vertigo are studied. Cochleovestibular symptoms and atherosclerotic potential risk factors were collected. Characteristics were studied with analysis of variance, chi2 test, or a paired t test. A receiver operating characteristic curve was obtained. A logistic regression with a step-wise selection based on the likelihood ratio was used to identify the best subgroup of predictors of the VS. RESULTS: The most revealing data were the mean ASNHL at 3,000 Hz (p < 0.001), the interaural SDS asymmetry (p < 0.001), the vestibular deficit (p < 0.049), and the absence of vertigo (p < 0.001). The ASNHL at 3,000 Hz was the most representative value of all the frequencies and for the SDS asymmetry. Interaural difference of 15 dB or more at 3,000 Hz is sufficient to consider hearing loss as asymmetric. When the cutoff for a positive test was placed at 50% probability, the receiver operating characteristic curve shows a sensitivity of 73%. The grade of the tumor was also related with the degree of ASNHL at 3,000 Hz. Caloric test does not predict the localization or the grade of the VS. Tinnitus and atherosclerotic potential risk factors were not considered significantly linked with
CONCLUSION: To reduce the number of negative MRI performed in the investigation of an ASNHL, we propose the "rule 3,000," ASNHL of 15 dB or more at the 3,000-Hz frequency. In this case, an investigation with MRI is crucial. If this ASNHL is less than 15 dB, we recommend a biannual audiometric follow-up. PMID: 19395982 [PubMed - in process]

The role of magnetic resonance imaging in the identification of suspected acoustic neuroma: a systematic review of clinical and cost effectiveness and natural history.


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OBJECTIVE(S): To evaluate the clinical effectiveness and cost-effectiveness of a range of diagnostic strategies for investigating patients with unilateral hearing loss and/or tinnitus, with a view to confirming or eliminating a diagnosis of acoustic neuroma, and to describe the natural history of acoustic neuroma.

DATA SOURCES: Major electronic databases were searched from January 1980 to August 2008.

REVIEW METHODS: Selected studies were assessed and subjected to data extraction and quality assessment using standard methods. RESULTS: Studies comparing auditory brainstem response (ABR) with magnetic resonance (MR) imaging were highly heterogeneous. ABR has high sensitivity compared with MR imaging for acoustic neuromas greater than 1 cm in size but not for smaller neuromas. The sensitivities of T2-weighted (T2W) and T2-star-weighted (T2*W) imaging strategies compared with gadolinium-enhanced T1-weighted (GdT1W) MR imaging (gold standard) were high and relatively homogeneous. The specificity of T2W and T2*W studies ranged from 90% to 100% and from 86% to 99% respectively. The review of cost-effectiveness showed that GdT1W MR imaging immediately or in conjunction with ABR appears to be more cost-effective than ‘traditional’ protocols; ABR/GdT1W MR imaging protocols were more cost-effective than going directly to GdT1W MR imaging. Non-contrast-enhanced MR imaging was found to be a more cost-effective test for acoustic neuroma than GdT1W MR imaging. The incidence of acoustic neuroma has increased over the last 30 years, with the median age at diagnosis remaining at 55 years. Most patients present with insidious symptoms of unilateral hearing impairment, tinnitus and/or vertigo. The pattern and rate of growth of acoustic neuroma are highly variable and currently unpredictable. At least 50% of tumours do not grow, at least for some years after diagnosis. Some studies have found large initial size to be a determinant of later growth, with the opposite also being reported. The mean growth rate for all tumours varies between 1 and 2 mm/year, with a rate of 2-4 mm/year for only those that grow; however, there are cases with significant regression (5%) or exceptional growth (which may exceed 18 mm/year). CONCLUSIONS: The majority of the evidence reviewed was poorly reported and there is therefore an inherent risk of bias. Given the recent improvement in resolution and reduction in cost of MR imaging, ABR can no longer be considered appropriate as the primary test used to screen for acoustic neuroma. T2W or T2*W sequences enable accurate evaluation of the VIIIth and VIIth cranial nerves within the cerebellopontine angle and internal auditory canal as well as evaluation of the cochlea and labyrinth, and inclusion of GdT1W sequences is unlikely to contribute information that would alter patient management in the screening population. The quality of the imaging chain and experience of the reporting radiologist are key factors determining the efficacy of a non-contrast screening strategy. Based on a cost-effectiveness model developed to reflect UK practice it was concluded that a diagnostic algorithm that deploys non-contrast MR imaging as an initial imaging screen in the investigation of acoustic neuroma is less costly than and likely to be as effective as available contrast MR imaging.
The value of CT venography in the diagnosis of jugular bulb diverticulum: a series of 3 cases.
Ear Nose Throat J. 2009 Apr;88(4):E4-7.

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Jugular bulb diverticulum is a rare diagnosis, as fewer than 50 cases have been reported in the literature. It has been reported that unilateral auditory symptoms may accompany this entity, although some patients are asymptomatic. We present a case series of 3 patients who were referred to our tertiary care neurotology center with a unilateral jugular bulb diverticulum along with unilateral sensorineural hearing loss and tinnitus. These patients were evaluated clinically and radiographically. This case series (1) adds further documentation of the presence of unilateral auditory symptoms in patients with a jugular bulb diverticulum and (2) demonstrates the value of computed tomograph venography in the diagnosis of jugular bulb diverticulum.

Idiopathic intracranial hypertension in otolaryngology.

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Idiopathic intracranial hypertension (IIH) is defined as increased intracranial pressure in the absence of intracranial mass or obstructive hydrocephalus. Over 80% of patients are overweight women. IIH is usually encountered in the neurology and ophthalmology practise as headaches, visual disturbance and papilloedema are the characteristic features of this syndrome. Patients with IIH also experience tinnitus, hearing loss, balance disturbance, cerebrospinal fluid (CSF) otorrhoea or rhinorrhoea and in some cases these otorhinological symptoms can be presenting features of this syndrome. IIH is also associated with obstructive sleep apnoea. Otolaryngologists should be familiar with this important condition as it can manifest a variety of symptoms that are more frequently seen in their clinics. Sometimes otolaryngologists may be involved in the surgical management of this condition, such as repair of CSF rhinorrhoea or otorrhoea or endoscopic optic nerve decompression. The aim of this review article is to familiarise the otolaryngologists with the important features of this unusual syndrome which may remain unrecognised in the otolaryngology practice.

Endovascular management of dural arteriovenous fistulas of the transverse and sigmoid sinus in 150 patients.

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INTRODUCTION: This study aimed to evaluate the safety and efficiency of the endovascular treatment of transverse-sigmoid sinus dural arteriovenous fistulas (TS_dAVF). METHODS: A total of 150 consecutive patients and 348 procedures were evaluated. RESULTS: Pulsatile tinnitus (81%), headache (15%), and intracranial hemorrhage (10%) were the most frequent manifestations of the TS_dAVFs. More than half of the affected sinuses were partially or completely thrombosed. Access-wise treatment was performed transarterial (n = 33), transvenous (n = 21), or a combination thereof (n = 96). A mean of 2.4 procedures per patient was required. Immediate postprocedural occlusion rate after transarterial embolization was 30% only. Transvenous treatment alone resulted in an early occlusion rate of 81%, with delayed complete obliteration of half of the remaining fistulas. After combined transarterial/transvenous treatment, the angiographic cure rate was 54%. At follow-up, 88% of patients with residual shunt after the treatment showed complete occlusion. The cumulative complication rate was 9% (n = 13), with minor adverse events in ten patients (7%) and major complications in three patients (2%). CONCLUSION: Transvenous coil occlusion of the sinus segment with the adjacent dAVF site, eventually combined with
transarterial occlusion of supplying arteries, is a very effective and well-tolerated treatment method. In selected patients, variations of these methods (e.g., sinus stenting, compartmental sinus occlusion) can be useful.

**Auditory manifestations of superior semicircular canal dehiscence.**


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OBJECTIVE: To understand the presenting auditory signs and symptoms and to examine the relationship between the auditory manifestations and audiometric parameters in superior semicircular canal dehiscence (SSCD). PATIENTS: Twenty consecutive patients with unilateral SSCD without a history of previous ontologic surgery. MAIN OUTCOME MEASURE: Relationship between presenting symptoms and the bone-conduction thresholds and air-bone gap (ABG) on pure-tone audiometry. RESULTS: All 20 patients presented with typical vestibular symptoms of SSCD. Seventeen (85%) patients also had auditory symptoms, including autophony (40%), hyperacusis to bodily sounds (65%), hearing loss (40%), aural pressure (45%), and tinnitus (35%). Of the 17 patients, 14 (82%) patients had an ABG on audiometry, but only 7 (41%) patients demonstrated negative bone conduction thresholds. Of 8 patients, 5 who underwent surgical repair experienced resolution of autophony and/or hyperacusis postoperatively. CONCLUSION: Auditory symptoms are common in SSCD patients. These symptoms do not show any relationship to the presence of negative bone-conduction thresholds on pure-tone audiometry. No firm conclusion could be drawn regarding the association between symptoms and ABG. Different pathways or mechanisms may exist in SSCD for bone-conducted sounds arising from different sources. Surgical repair of the dehiscence results in resolution of auditory symptoms in most patients.

**Polycythemia vera in Nigeria.**


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BACKGROUND: There is a paucity of reports on polycythemia vera (PV) in Nigeria. The aim of this review is to present the pattern of clinical presentation, method of diagnosis, therapeutic options and treatment outcome in the face of limited facilities. MATERIALS AND METHODS: Case notes of patients with confirmed diagnosis of PV managed at the Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC), Ile-Ife, Nigeria from 1997 to 2006, were reviewed for clinical and laboratory parameters. The relative proportion of PV to other cases of hematologic cancers seen within the same period was determined. RESULTS: Seven patients, 5 males and 2 females, aged 42-70 years (median, 53 years) were studied. All the patients were symptomatic at diagnosis with the majority presenting with headaches, visual disturbances, and tinnitus. Clinical signs include conjunctival suffusion in all the patients; splenomegaly, hepatomegaly and hypertension in 3 patients (42.8%). Pruritus was uncommon (14.3%). One patient (14.3%) presented with fatal cerebrovascular accident on admission. The average follow up period was 39.9 months, and 2 patients (28.6%) were followed up for more than 7 years. Therapy consisted mainly of regular phlebotomy and low dose aspirin for suppression of thromboxane synthesis and control of thrombocytosis and erythromelalgia. PV accounts for just 0.03% of all the hematologic cancers seen. CONCLUSION: PV has a low incidence in our population and affects significantly the middle age persons. The clinical presentation consisted of headaches, visual disturbance, hypertension, and organomegaly. Treatment outcome are not different from those previously reported. The need for life-long follow up must be emphasised to patients at diagnosis.
IV Imaging

Neural activity underlying tinnitus generation: Results from PET and fMRI.
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Tinnitus is the percept of sound that is not related to an acoustic source outside the body. For many forms of tinnitus, mechanisms in the central nervous system are believed to play an important role in the pathology. Specifically, three mechanisms have been proposed to underlie tinnitus: (1) changes in the level of spontaneous neural activity in the central auditory system, (2) changes in the temporal pattern of neural activity, and (3) reorganization of tonotopic maps. The neuroimaging methods fMRI and PET measure signals that presumably reflect the firing rates of multiple neurons and are assumed to be sensitive to changes in the level of neural activity. There are two basic paradigms that have been applied in functional neuroimaging of tinnitus. Firstly, sound-evoked responses as well as steady state neural activity have been measured to compare tinnitus patients to healthy controls. Secondly, paradigms that involve modulation of tinnitus by a controlled stimulus allow for a within-subject comparison that identifies neural activity that may be correlated to the tinnitus percept. Even though there are many differences across studies, the general trend emerging from the neuroimaging studies, is that tinnitus in humans may correspond to enhanced neural activity across several centers of the central auditory system. Also, neural activity in non-auditory areas including the frontal areas, the limbic system and the cerebellum seems associated with the perception of tinnitus. These results indicate that in addition to the auditory system, non-auditory systems may represent a neural correlate of tinnitus. Although the currently published neuroimaging studies typically show a correspondence between tinnitus and enhanced neural activity, it will be important to perform future studies on subject groups that are closely matched for characteristics such as age, gender and hearing loss in order to rule out the contribution of these factors to the abnormalities specifically ascribed to tinnitus.

Loss of alpha power is related to increased gamma synchronization-A marker of reduced inhibition in tinnitus?

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Tinnitus is the perception of sound in the absence of any external auditory stimulus. Based on previous research we have proposed a framework which postulates that the reduction of ongoing inhibitory alpha activity in tinnitus subjects favors a synchronization of neurons in the gamma frequency range while in a resting state. In the present work we are validating the existence of an inverse relationship between auditory gamma and alpha activity in tinnitus and control subjects using Magnetoencephalography. Tinnitus subjects exhibited a significantly steeper slope of the regression line compared to controls, presumably because a greater number of subjects concurrently exhibited low alpha and high gamma power. Therefore, the role of the alpha-gamma pattern is discussed regarding its possible implication for the generation of tinnitus.

Structural brain changes in tinnitus: grey matter decrease in auditory and non-auditory brain areas.

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Tinnitus, the phantom perception of sound, is a frequent disorder that causes significant morbidity. The pathophysiological mechanisms involved in tinnitus generation are still under exploration. Electrophysiological and functional neuroimaging studies give increasing evidence for abnormal functioning both within the central auditory system and in non-auditory brain areas. However, observed changes show great variability, hence lacking a conclusive picture. Recently, structural alterations in the central nervous system have been detected in tinnitus patients by voxel-based morphometry (VBM). Here we aimed to replicate these findings in an independent study sample. We performed structural MRI scans in 28 tinnitus patients with normal audiometry and used VBM to compare results with a control group, matched for age, sex and hearing status. As major results we found significant grey matter decreases in the tinnitus group in the right inferior colliculus and in the left hippocampus. However, neither changes in the subcallosal area nor in the thalamus as described recently have been observed. Our results underscore that (1.) VBM allows to detect structural alterations in tinnitus patients, which seem to be related to tinnitus pathophysiology. (2.) Both, areas in the auditory and the limbic system are involved giving further evidence for the important role of the limbic system in the pathophysiology of tinnitus. (3.) Even groups with similar clinical characteristics might differ in the underlying neurobiological changes.

The mechanisms of tinnitus: perspectives from human functional neuroimaging.

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In this review, we highlight the contribution of advances in human neuroimaging to the current understanding of central mechanisms underpinning tinnitus and explain how interpretations of neuroimaging data have been guided by animal models. The primary motivation for studying the neural substrates of tinnitus in humans has been to demonstrate objectively its representation in the central auditory system and to develop a better understanding of its diverse pathophysiology and of the functional interplay between sensory, cognitive and affective systems. The ultimate goal of neuroimaging is to identify subtypes of tinnitus in order to better inform treatment strategies. The three neural mechanisms considered in this review may provide a basis for TI classification. While human neuroimaging evidence strongly implicates the central auditory system and emotional centres in TI, evidence for the precise contribution from the three mechanisms is unclear because the data are somewhat inconsistent. We consider a number of methodological issues limiting the field of human neuroimaging and recommend approaches to overcome potential inconsistency in results arising from poorly matched participants, lack of appropriate controls and low statistical power.

V Pharmacotherapy

Management of tinnitus: oral treatment with melatonin and sulodexide.

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The main problem arising from tinnitus is the disturbance it causes in day-to-day life and disturbance in sleep leading to fatigue and general discomfort. We attempted to study the effect of melatonin in conjunction with Sulodexide as a treatment method for tinnitus and evaluate its effectiveness. We studied 102 patients suffering from tinnitus with a Prospective Randomised Controlled Study conducted in a tertiary care ENT department. After randomisation, 34 patients were treated with melatonin and Sulodexide, another 34 were treated with melatonin alone, and the remaining 34 (control group) were managed without therapy in order to evaluate spontaneous variations in quality of tinnitus. Patients were assessed prospectively with Tinnitus Handicap Inventory and Acufenometry both pre-treatment and post-treatment. Among the patients we studied, we found better results with both Tinnitus Handicap Inventory
and Acufenometry in the group who received melatonin and Sulodexide as against melatonin alone. Any improvement was noted in the control group. In conclusion, our opinion is that melatonin in combination with Sulodexide is a viable treatment option for patients suffering from central or sensorineural tinnitus.

**Tinnitus Treatment With Piribedil Guided by Electrocochleography and Acoustic Otoemissions.**

*Otol Neurotol. 2009 Jul 1. [Epub ahead of print]*

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**INTRODUCTION:** Tinnitus is a frequent disorder and very difficult to treat. Both animal studies and clinical observations suggest that dopaminergic substances might have potential for the treatment of tinnitus. Here, we investigated the dopamine agonist piribedil for the treatment of chronic tinnitus. In all participants, we performed audiometry, electrocochleography (ECoG), and otoacoustic emissions before treatment began. OBJECTIVE: To assess the efficacy and safety of the dopaminergic drug piribedil for the treatment of tinnitus and to evaluate whether ECoG and acoustic otoemissions might be useful for predicting treatment response. STUDY DESIGN: Prospective randomized double-blind crossover study. SUBJECTS AND METHOD: One hundred patients with tinnitus were randomized into a double-blind, placebo-controlled, prospective crossover study. All patients underwent distortion product acoustic otoemissions with and without contralateral suppression and ECoG. Patients received 50 mg piribedil and placebo for 90 days each, separated by a 30-day washout period. Treatment effects were assessed by using the Tinnitus Handicap Inventory and a visual analog scale. Fifty-six patients completed the trial. RESULTS: There was no significant improvement of Tinnitus Handicap Inventory and visual analog scale score after piribedil treatment as compared with placebo. However, results were characterized by high interindividual variability. Post hoc analysis of piribedil effects revealed that piribedil treatment responders differed from nonresponders by the occurrence of a double peak in the ECoG. In addition, normal distortion product acoustic otoemission suppression patterns indicated better treatment response with piribedil. The incidence of side effects during piribedil treatment was 23.3%, leading to interruption of treatment in all cases. CONCLUSION: Piribedil is not superior to placebo in the treatment of tinnitus. Piribedil treatment responders differed from nonresponders by specific findings in the ECoG and in the distortion product acoustic otoacoustic emissions, suggesting a beneficial effect of piribedil in an electrophysiologically characterized tinnitus subgroup. CLINICAL TRIAL REGISTRY: The study has been registered in ClinicalTrials.gov under the number NCT00591994.

**The NGF point-injection for treatment of the sound-perceiving nerve deafness and tinnitus in 68 cases.**


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**OBJECTIVE:** To observe the therapeutic effects of the point-injection with nerve growth factor (NGF) for the sound-perceiving nerve deafness and tinnitus. METHODS: The 140 cases in this series were randomly divided into a treatment group of 68 cases treated by NGF injection at the points of Yifeng (TE 17) and Wangu (GB 12), and a control group of 72 cases orally taking Xibiling and adenosine triphosphate (ATP) and intramuscular injection with VB1 and VB12. RESULTS: The total effective rate was 78.6% in the treatment group and 31.8% in the control group, with significant difference between the two groups (P<0.05). CONCLUSION: For treating nervous deafness and tinnitus, NGF point-injection may show good therapeutic effects, but inversely proportional to the illness course, age and the extent of hypoacusis.
Kunel'skaya NL, Levin YV, Krasyuk AA, Doronina OM.

The objective of the study was to evaluate efficacy and tolerance of tanakan during treatment of neurosensory hearing loss and subjective tinnitus supposedly of vascular etiology. The secondary purpose was to analyse late results of 3 month courses of therapy and changes in the clinical course of the disease during treatment and within 6 months after its termination. Tanakan was first given at a dose of 40 mg thrice daily for 90 days. Results of the treatment were estimated on days 90, 180, and 240. The second course (40 mg thrice daily for 90 days) was initiated 180 days after the end of the first one. The final outcome was evaluated on day 360. It was shown that monotherapy with tanakan effectively improved the hearing function and had the most pronounced beneficial effect on subjective tinnitus. Results of the treatment remained stable throughout the entire observation period (12 months).

The nicotinic receptor of cochlear hair cells: A possible pharmacotherapeutic target?

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Mechanosensory hair cells of the organ of Corti transmit information regarding sound to the central nervous system by way of peripheral afferent neurons. In return, the central nervous system provides feedback and modulates the afferent stream of information through efferent neurons. The medial olivocochlear efferent system makes direct synaptic contacts with outer hair cells and inhibits amplification brought about by the active mechanical process inherent to these cells. This feedback system offers the potential to improve the detection of signals in background noise, to selectively attend to particular signals, and to protect the periphery from damage caused by overly loud sounds. Acetylcholine released at the synapse between efferent terminals and outer hair cells activates a peculiar nicotinic cholinergic receptor subtype, the alpha9alpha10 receptor. At present no pharmacotherapeutic approaches have been designed that target this cholinergic receptor to treat pathologies of the auditory system. The potential use of alpha9alpha10 selective drugs in conditions such as noise-induced hearing loss, tinnitus and auditory processing disorders is discussed.

Treatment of subjective tinnitus: a comparative clinical study of intratympanic steroid injection vs. oral carbamazepine.


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BACKGROUND: Over the last decade, more and more otologists have been using the intratympanic perfusion of steroids to treat SSHL, tinnitus, and vertigo. However, results of the treatment in the literature are controversial because most of the reports were retrospective and uncontrolled. Therefore a prospective random single-blind trial was conducted at the Affiliated Drum Tower Hospital of Nanjing University Medical School, P. R. China. The results were compared with oral carbamazepine treatment. Carbamazepine is a medication routinely used to treat tinnitus. MATERIAL/METHODS: Seventy-nine patients (84 ears) with subjective tinnitus which failed to respond to a minimum of four-week systemic medical therapy were assigned to a study group and a control group by a random, single-blind method. The study group was further randomly divided into two subgroups. The participants in the study group received either 0.5-ml intratympanic injections of prednisolone (study group 1) or dexamethasone (study group 2). The patients in the control group only took carbamazepine. The effective rates at the
RESULTS: There were no statistical differences in the effective and control rates among the three groups. CONCLUSIONS: Intratympanic steroid injection has positive effects similar to those of oral carbamazepine in subjective tinnitus. Intratympanic steroid injection may be considered an alternative treatment for subjective tinnitus.

Gabapentin responsive audiovestibular paroxysmia.
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Trigeminal neuralgia and hemifacial spasm are well-documented vascular compression syndromes involving the 5th and 7th cranial nerves. Drugs that stabilize the irritated nerves and vascular decompression surgery are accepted treatments. By contrast, the diagnosis and treatment of a comparable syndrome involving the 8th cranial nerve is controversial. We describe two patients with brief, spontaneous, recurrent attacks of tinnitus and vertigo that responded to low dose gabapentin and we argue that this clinical presentation represents the prototypical 8th nerve vascular compression syndrome.

VI Auditive Stimulation

Tinnitus distress, anxiety, depression, and hearing problems among cochlear implant patients with tinnitus.
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BACKGROUND: While several studies have investigated the presence and annoyance of tinnitus in cochlear implant (CI) recipients, few studies have probed the handicap associated with tinnitus in this population. PURPOSE: The aim of this study was to use validated self-report measures in a consecutive sample of CI patients who reported tinnitus to determine the extent of tinnitus handicap. RESEARCH DESIGN: In a retrospective design, a total of 151 patients (80% response rate) reported to a postal questionnaire, and of these, 111 (74%) reported that they currently experienced tinnitus and were asked to complete the full questionnaire. Sampling was performed at a point of a mean 2.9 years postsurgery (SD = 1.8 years). Three established self-report questionnaires were included measuring tinnitus handicap (Tinnitus Handicap Inventory [THI]), hearing problems (Gothenburg Profile), and finally, a measure of anxiety and depression (Hospital Anxiety and Depression Scale). We analyzed the data by means of Pearson product moment correlations, t-tests, ANOVAs, and chi-square. RESULTS: Data from the validated questionnaires showed relatively low levels of tinnitus distress, moderate levels of hearing problems, and low scores on the anxiety and depression scales. Using the criteria proposed for the THI (which was completed by 107 patients), 35% (N = 38) had a score indicating “no handicap,” 30% (N = 32) “mild handicap” 18% (N = 19) “moderate handicap,” and 17% (N = 18) “severe handicap.” Thus 37 individuals from the total series of 151 reported moderate to severe tinnitus handicap (24.5%). Tinnitus distress was associated with increased hearing problems, anxiety, and depression. CONCLUSION: Tinnitus can be a significant problem following CI, but that the experienced distress is often moderate. However, a quarter of CI recipients do demonstrate moderate/severe tinnitus handicap, and thus are candidates for tinnitus specific therapy. The level of tinnitus handicap is associated with hearing problems and psychological distress.
Effects of hearing aid fitting on the perceptual characteristics of tinnitus.

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Restoration of auditory input through the use of hearing aids has been proposed as a potentially important means of altering tinnitus among those tinnitus sufferers who experience significant sensorineural hearing loss. In animal models of neural plasticity induced by noise trauma, high-frequency stimulation in deafferented regions of the auditory spectrum has been shown to modulate cortical reorganization after hearing loss, a result which suggests that the neural basis of tinnitus is subject to interference by acoustic stimulation. This study drew on deafferentation models to investigate the effect of hearing aids on the psychoacoustic properties of the tinnitus sensation, using both conventional amplification and high-bandwidth amplification regimes. The tinnitus percept was affected only weakly in the conventional amplification group, and was not at all affected in the high-bandwidth group. The changes observed under conventional, low-to-medium frequency amplification may indicate that the perceptual characteristics of tinnitus depend on the pattern of sensory inputs - notably a contrast in activity between adjacent central auditory regions of more and less afferent activity - while the absence of modifications in the high-bandwidth amplification group suggests limit on the tractability of the tinnitus percept. This limit to the malleability of the tinnitus percept may arise from either the extent of hearing deficits or the duration and robustness of the neuroplastic changes that originally give rise to tinnitus.

Complications and Pitfalls of Cochlear Implantation in Otosclerosis: A 6-Year Follow-Up Cohort Study.
Otol Neurotol. 2009 Apr 23.

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OBJECTIVE: To describe and discuss the midterm complications and pitfalls reported in patients with otosclerosis who received a cochlear implant. STUDY DESIGN:: Prospective cohort study. SETTING:: Tertiary referral center. PATIENTS:: Fifteen patients who received a cochlear implant for otosclerosis, followed up for a minimum of 6 years. Onset of hearing loss occurred at a mean age (+/-standard deviation [SD]) of 32.6 +/- 8.6 years. Mean duration (+/-SD) of hearing loss was 26.8 +/- 7.9 years, and mean age (+/-SD) at implant surgery was 58.7 +/- 9.5 years. INTERVENTIONS:: Before cochlear implantation, hearing thresholds were tested, and temporal bone anatomy and otosclerotic lesions were documented by high-resolution computed tomography and magnetic resonance imaging. All patients were implanted with a Med-El Combi 40 + device and a Standard Electrode Array. MAIN OUTCOME MEASURES: The number of inserted electrodes was checked by x-ray. After cochlear implantation, hearing skills were tested, fitting parameters were recorded, and complications were noted. RESULTS:: As the disease progressed, the number of electrodes decreased, and the electrical thresholds, maximum comfort levels, and electric charge increased; these changes were more evident in the middle electrodes. Although facial nerve stimulation rate was lower than previously reported (13.3%), it increased during follow-up. Two patients (13.3%) had untreatable tinnitus. Nevertheless, all speech discrimination parameters improved significantly in all patients. CONCLUSION: Despite the need for special fitting strategies and the appearance of complications, facial nerve stimulation, and tinnitus, improvements in speech discrimination tests support the use of cochlear implantation for patients with otosclerosis.
Are results of tinnitus retraining therapy maintained over time? 18-month follow-up after completion of therapy.

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Tinnitus retraining therapy (TRT) is a useful treatment for tinnitus. The aim of this study was to evaluate the results obtained after 18 months of TRT as well as 18 months after completion of therapy, i.e. 36 months after initiation of TRT. Forty-five subjects suffering from an idiopathic tinnitus with or without hyperacusis for at least 6 months were recruited. There were significant improvements during therapy (p < 0.001) and the mean Tinnitus Handicap Inventory (THI) was lowered by more than 20 points. These improvements persisted 18 months after treatment completion. Furthermore, the percentage of patients reporting the disappearance of their difficulties in various activities (relaxation, concentration, sleep, social relations and work) increased continuously after treatment completion. TRT improved self-perceived disability induced by chronic tinnitus for a long time after the end of therapy. Copyright (C) 2009 S. Karger AG, Basel.

Spiral ganglion cell loss is unrelated to segmental cochlear sensory system degeneration in humans.
Otol Neurotol. 2009 Apr;30(3):418-422.

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OBJECTIVE: To demonstrate that contrary to what occurs in animals, neuron loss in the human spiral ganglion is not in proportion to organ of Corti hair or supporting cell loss. STUDY DESIGN: Histopathological review of archival temporal bone histological sections. SETTING: Nonprofit research facility. METHODS: Four temporal bones, from an archival collection of 1,448 temporal bones, were found that had a total loss of hair and supporting cells limited to the basal segment of the cochlea and a hearing loss of 3 or more years (range, 3-28 yr). Cochlear reconstructions were conducted to demonstrate the populations of hair and supporting cells, peripheral processes (dendrites), spiral ganglion cells, and the amount of surviving stria vascularis in different cochlear segments. RESULTS: The total loss of hair and supporting cells of the organ of Corti in the base of the cochlea is not accompanied by a proportional loss of spiral ganglion cells in the modiolar base. CONCLUSION: A long-term loss of hearing in frequencies greater than 2 kHz, and corresponding hair cell loss, does not result in a subsequent loss of spiral ganglion cells in humans, in contrast to what has been reported in association with animals. These findings suggest that the poor performance of cochlear implant in patients after prolonged deafness is not caused by ongoing degeneration of ganglion cells.

VII Brain Stimulation

Repetitive transcranial magnetic stimulation improve tinnitus in normal hearing patients: a double-blind controlled, clinical and neuroimaging outcome study.
Eur J Neurol. 2009 Jul 9. [Epub ahead of print]

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Background and purpose: Tinnitus is a frequent disorder which is very difficult to treat and there is compelling evidence that tinnitus is associated with functional alterations in the central nervous system. Targeted modulation of tinnitus-related cortical activity has been proposed as a promising new treatment approach. We aimed to investigate both immediate and long-term effects of low frequency (1 Hz) repetitive transcranial magnetic stimulation (iTMS) in patients with tinnitus and normal hearing. Methods: Using a parallel design, 20 patients were randomized to receive either active or placebo stimulation over
the left temporoparietal cortex for five consecutive days. Treatment results were assessed by using the Tinnitus Handicap Inventory. Ethyl cysteinate dimmer-single photon emission computed tomography (SPECT) imaging was performed before and 14 days after rTMS. Results: After active rTMS there was significant improvement of the tinnitus score as compared to sham rTMS for up to 6 months after stimulation. SPECT measurements demonstrated a reduction of metabolic activity in the inferior left temporal lobe after active rTMS. Conclusion: These results support the potential of rTMS as a new therapeutic tool for the treatment of chronic tinnitus, by demonstrating a significant reduction of tinnitus complaints over a period of at least 6 months and significant reduction of neural activity in the inferior temporal cortex, despite the stimulation applied on the superior temporal cortex.

**Does a single session of theta-burst transcranial magnetic stimulation of inferior temporal cortex affect tinnitus perception?**


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BACKGROUND: Cortical excitability changes as well as imbalances in excitatory and inhibitory circuits play a distinct pathophysiological role in chronic tinnitus. Repetitive transcranial magnetic stimulation (rTMS) over the temporoparietal cortex was recently introduced to modulate tinnitus perception. In the current study, the effect of theta-burst stimulation (TBS), a novel rTMS paradigm was investigated in chronic tinnitus. Twenty patients with chronic tinnitus completed the study. Tinnitus severity and loudness were monitored using a tinnitus questionnaire (TQ) and a visual analogue scale (VAS) before each session. Patients received 600 pulses of continuous TBS (cTBS), intermittent TBS (iTBS) and intermediate TBS (imTBS) over left inferior temporal cortex with an intensity of 80% of the individual active or resting motor threshold. Changes in subjective tinnitus perception were measured with a numerical rating scale (NRS). RESULTS: TBS applied to inferior temporal cortex appeared to be safe. Although half of the patients reported a slight attenuation of tinnitus perception, group analysis resulted in no significant difference when comparing the three specific types of TBS. Converting the NRS into the VAS allowed us to compare the time-course of aftereffects. Only cTBS resulted in a significant short-lasting improvement of the symptoms. In addition there was no significant difference when comparing the responder and non-responder groups regarding their anamnestic and audiological data. The TQ score correlated significantly with the VAS, lower loudness indicating less tinnitus distress. CONCLUSION: TBS does not offer a promising outcome for patients with tinnitus in the presented study.

**Theta burst stimulation in the treatment of incapacitating tinnitus accompanied by severe depression.**

CNS Spectr. 2009 Apr;14(4):208-211.

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This case report describes the use of transcranial magnetic theta burst stimulation (TBS) in the treatment of incapacitating tinnitus accompanied by symptoms of severe depression. Tinnitus is known to be associated with hyperactivity and maladaptive cortical reorganization of the central auditory system. Combined with anxiety and depression, it can occasionally constitute a psychiatric emergency. Recently, it has been demonstrated that tinnitus can be temporarily suppressed by non-invasive transcranial magnetic stimulation. TBS is a newly developed technique for rapid and lasting modulation of cortical excitability. Herein, we present a case of a 54-year-old woman with incapacitating tinnitus that has significantly decreased after three cycles of 1-week treatment with continuous TBS to the temporoparietal auditory association cortex. According to the Tinnitus Questionnaire, tinnitus intensity decreased from 84 points before to 59 points after treatment. Hamilton Rating Scale for Depression score dropped from 44 to 23 points. TBS showed to be efficient, well-tolerated, and practical in the management of distressing tinnitus accompanied by symptoms of severe depression.
[Effect of electrical stimulation of the primary auditory cortex on the spontaneous activities of the external nucleus of the inferior colliculus in a rat model of tinnitus induced by salicylate acid.]

[Article in Chinese]
Sheng Li Xue Bao. 2009 Apr 25;61(2):121-126.

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This study aims to investigate corticofugal modulation on spontaneous activities of the external nucleus of the inferior colliculus (ICx) in a salicylate acid (SA) induced tinnitus rat model by the stimulation of the primary auditory cortex (AI). Extracellular recording techniques and stereotaxic method were used. The spontaneous activities of a single unit were recorded from the left ICx after electrical stimulation was given to the left AI of the rats duplicated as acute SA models. The average rate of spontaneous discharge and the interspike interval histogram of spontaneous activities were used as indices. The single unit spontaneous discharges of the same unit of ICx before and after AI stimulation were observed. There was an inhibitory effect of AI stimulation on the activities of the high discharge unit [(8.75+/-2.70) Hz vs (5.06+/-2.01) Hz] and a facilitatory effect on the low discharge unit [(1.41+/-0.45) Hz vs (2.46+/-0.79) Hz]. In the normal group, there was a restraining effect on the average rate of spontaneous discharge of the ICx after AI stimulation. The average rate of spontaneous discharge changed from (3.66+/-0.84) Hz to (2.47+/-0.43) Hz in the first hour after AI stimulation and then recovered within 2-4 h. And the discharge rate of the spike interval within 0-20 ms decreased (17% vs 7.3%, 11.2%) in the first 2 h and recovered 3-4 h after AI stimulation. The discharge rate of the spike interval within 0-6 ms (short interval) recovered 2 h after AI stimulation. In the acute SA model group, the average rate of spontaneous discharge recorded from the ICx decreased from (7.48+/-0.85) Hz to (3.38+/-0.39) Hz in the first hour after AI stimulation and the suppression effect remained 4 h (P<0.05). There was no difference in the average rate of spontaneous discharge between the acute SA model group and the normal group at 2-4 h after AI stimulation. The suppression effect on the 0-20 ms interval spikes in the ICx lasted 4 h, while that on the shorter interval (0-6 ms) spikes recovered in the 3rd hour after AI stimulation. It might be inferred that stimulation of AI, through exciting the auditory descending projections, could remit the increased spontaneous discharge of ICx induced by SA that may relate with tinnitus in a period of time.

**VIII Behavioral Therapy**

**Effectiveness of a tinnitus management programme: a 2-year follow-up study.**


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**BACKGROUND:** Tinnitus impairs the possibility of leading a normal life in 0.5-1% of the population. While neither medical nor surgical treatment appears effective, counselling may offer some relief. An intervention combining counselling and hearing devices is offered to clients referred to the Centre for Help Aids and Communication (CHC) in southern Denmark. The aims of this exploratory study were to examine i) the characteristics of CHC’s clients and their tinnitus, ii) the effectiveness of the treatment, and iii) whether particular client groups benefit more than others. **METHODS:** One hundred new clients presenting with tinnitus completed the Tinnitus Handicap Inventory (THI) three times - before their first consultation, after one month and after 1-2 years. The scores were tested for significant differences over time using tests for paired data. Logistic regression was used to examine factors associated...
with a clinically important difference (i.e. THI score improvement of at least 20 points). RESULTS: At final follow-up, total THI score was significantly lower than baseline, i.e. 29.8 (CI 25.5-34.2) vs. 37.2 (CI 33.1-37.2), p<0.01, as were the three subscale scores. The programme achieved a clinically important difference for 27% and 24% of the clients one month and 1-2 years after the first consultation, respectively. It appeared that greater improvement in THI score was related to higher baseline THI score and possibly also to treatment by a particular CHC therapist. The absolute reduction in mean THI score after 1-2 years for clients with moderate and severe handicap was 14 and 20 points, respectively, i.e. similar to that previously reported for TRT (14-28 points). The cost of the current programme was approximately 200 EUR per client. CONCLUSIONS: The tinnitus management programme appeared to provide significant benefit to many clients at a relatively low cost. It would be useful to conduct a randomised controlled study comparing the current programme with alternative forms of combination counselling/sound therapy approaches.

**Personal experience with tinnitus retraining therapy.**
Eur Arch Otorhinolaryngol. 2009 Jun 19.

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We present the results of tinnitus retraining therapy (TRT) in a group of patients suffering from tinnitus and/or hyperacusia. Based on the scores from a specific questionnaire and the Tinnitus Handicap Inventory (THI), the patients were classified into five categories and began therapy according to Jastreboff’s criteria. Depending on the individual case, therapy envisaged counselling sessions, ambient sound enrichment, sound generators and hearing aids. At the end of the 18-month period, therapeutic success was observed in 79% of the patients. The initial numerical values of the scale of the symptoms and the THI seem predictive of treatment outcome. The use of instruments (sound generators) increases the success rate, but the study also demonstrates the effectiveness of counselling and ambient sound enrichment. Failures mainly involved patients with hypacusia who refused to wear hearing aids, as this influenced the effectiveness of ambient sound enrichment and counselling. Paralleling the data in the literature, the results demonstrate the effectiveness of TRT, which cannot be attributed to a placebo effect given the extended duration of treatment.

**The tinnitus intensive therapy habituation program: a 2-year follow-up pilot study on subjective tinnitus.**
Rehabil Psychol. 2009 May;54(2):133-137.

**Bessman P, Heider T, Wattan VP, Watten RG.**
Alfred-Döblin-Strasse.

OBJECTIVES: To explore the effects of a new tinnitus treatment program (tinnitus intensive therapy [TIT]) based on auditory perception principles and neural habituation. METHODS: A follow-up study with measurement of treatment effects every third month over a 2-year period in which the cases were their own controls. PARTICIPANTS: There were 25 participants with a mean age 50.1 years (SD = 16.1); 10 women (52.7 years; SD = 16.8) and 15 men (48.3 years; SD = 15.9). The participants were recruited from clinical population admitted to a polyclinic tinnitus treatment program in western Germany. RESULTS: There was a significant reduction of tinnitus in the follow-up period. Mean baseline tinnitus scores (Tinnitus Fragebogen; Goebel & Hiller, 1998) at the start of the treatment were 50.9 (SD = 14.5) and the final scores were 14.2 (SD = 5.9). In total, the clinical improvement over the follow-up period was 72.1%. CONCLUSION: The TIT program showed a significant clinical treatment effect and should be tested further in a multicenter treatment project. The findings support the Jastreboff habituation model of tinnitus, but social cognitive factors should also be taken into account. (PsycINFO Database Record (c) 2009 APA, all rights reserved).
Are results of tinnitus retraining therapy maintained over time? 18-month follow-up after completion of therapy.

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Tinnitus retraining therapy (TRT) is a useful treatment for tinnitus. The aim of this study was to evaluate the results obtained after 18 months of TRT as well as 18 months after completion of therapy, i.e. 36 months after initiation of TRT. Forty-five subjects suffering from an idiopathic tinnitus with or without hyperacusis for at least 6 months were recruited. There were significant improvements during therapy (p < 0.001) and the mean Tinnitus Handicap Inventory (THI) was lowered by more than 20 points. These improvements persisted 18 months after treatment completion. Furthermore, the percentage of patients reporting the disappearance of their difficulties in various activities (relaxation, concentration, sleep, social relations and work) increased continuously after treatment completion. TRT improved self-perceived disability induced by chronic tinnitus for a long time after the end of therapy. Copyright (C) 2009 S. Karger AG, Basel.

IX Somatic Tinnitus

Systematic assessment of the impact of oral appliance therapy on the temporomandibular joint during treatment of obstructive sleep apnea: long-term evaluation.
Sleep Breath. 2009 May 1.

Giannasi LC, Almeida FR, Magini M, Costa MS, de Oliveira CS, de Oliveira JC, Kalil Bussadori S, de Oliveira LV.
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OBJECTIVE: The aim of the present study was to evaluate the symptoms of temporomandibular dysfunction (TMD) in patients with obstructive sleep apnea treated with long-term use of an oral appliance (OA) using a questionnaire based on the Helkimo Anamnestic Dysfunction Index. A further aim of the study was to evaluate the presence of daytime sleepiness using the Epworth Sleep Scale (ESS) and otologic symptoms. MATERIALS AND METHODS: Polysomnograms of 34 patients were performed at baseline and after 6 months of OA use. As follow-up, the patients were contacted by telephone interview to answer the same questionnaires after 36.0 +/- 17.0 months. RESULTS AND DISCUSSION: The intensity of TMD symptoms decreased significantly throughout treatment (p < 0.01). ESS values improved from 12.2 +/- 5.0 to 6.9 +/- 2.6 (p <= 0.05). Tinnitus was present in nine patients at baseline and decreased in intensity in seven patients by the final assessment while remaining at the same level in two patients. CONCLUSIONS: We conclude that long-term usage of an OA does not cause impairment to the temporomandibular joint. The Helkimo and otologic indexes are simple and useful in long-term patient follow-up. There was a long-term improvement in the ESS values over the years analyzed. A follow-up program could increase compliance by motivating patients to use the device regularly.

X Surgical Treatment

Middle ear adenomatous tumor: A not so rare glomus tympanicum-mimicking lesion.

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BACKGROUND AND PURPOSE: Middle ear adenomatous tumors (MEAT) are rare tumors which can be begin or malignant and can present a neuroendocrine differentiation. Their radiological aspect is very
similar to glomus tympanicum (GT) which are the most common tumoral lesions of the middle ear. We present several radiological and clinical findings that could help radiologists to accurately identify MEAT.

MATERIAL AND METHODS: We retrospectively reviewed the radiological and clinical findings of three patients with MEAT and of eight patients with GT. Diagnostic was obtained after surgical resection in all cases. All patients had high resolution CT and MR of the middle ear associated with a subtracted digital carotid angiography. Tumor location, size, extension, signal intensity, and enhancement were analysed. From the medical records of the patients, clinical manifestations (hearing loss, tinnitus), evolution length and recurrences were noted. RESULTS: MEAT and GT appeared as tissular lesion with significant enhancement on CT and MR. A vascular blush was present on angiography in all cases of GT and absent from all cases of MEAT. A close relationship between the tumor and the Jacobson’s nerve or its branches was identified in all cases of GT. Pulsatile tinnitus was present in all patients with GT and absent in all patients with MEAT. CONCLUSION: A middle ear tissular lesion clearly separated from the Jacobson nerve or its branches, showing significant enhancement after contrast medium injection but with a normal angiography, should make one suspicious for MEAT.

**Short and Long Term Results of Endolymphatic Sac Surgery: A Patient-Questionnaire Based Study.**

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INTRODUCTION: The endolymphatic sac surgery for the treatment of Meniere’s disease has been described since the 1920s. The success rate of this technique in terms of vertigo control has been reported to be 50-80%. However, the value of this treatment method remained controversial. Furthermore, the reliable identification of the endolymphatic sac intraoperatively can be challenging in some cases. This study examines the short-, middle- and long-term results in a larger cohort of patients. MATERIALS AND METHODS: In 74 patients, vertigo control, tinnitus and degree of satisfaction was evaluated by means of a questionnaire retrospectively. Additionally, the diagnostic value of the electrocochleography (EcochG) was determined. RESULTS: The overall vertigo control rate was more than 70% in patients followed up for two years and has reached 81% in patients followed up for more than two years. Hearing preservation rate was 61%. Tinnitus has disappeared in 11% and improved in 23% of the patients. In 47% of the patients it was unchanged and in 19% worsened. The difference in EcochG results pre- versus postoperative was highly significant. CONCLUSIONS: ELSS is a useful tool in the management of Ménière’s disease, in particular in patients that do not benefit sufficiently from conservative therapy.

**Vertebral artery stent graft for a chronic symptomatic vertebrojugular arteriovenous fistula.**

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A patient with a chronic, symptomatic V2 segment vertebrojugular fistula was successfully treated with a vertebral artery stent graft, with immediate tinnitus resolution. No early or late complications were observed, and at 45 months of follow-up, the patient remains asymptomatic with a patent stent graft. The existing literature on stent graft treatment of vertebrojugular fistula is reviewed.

**Effect of tumor removal on tinnitus in patients with vestibular schwannoma.**
J Neurosurg. 2009 May 29. [Epub ahead of print]
Kameda K, Shono T, Hashiguchi K, Yoshida F, Sasaki T.
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Object Tinnitus is one of the most common symptoms in patients with vestibular schwannomas (VSSs), but the effect of surgery on this symptom has not been fully evaluated. The aim of this study was to define the effect on tinnitus of tumor removal, cochlear nerve resection, and useful hearing preservation in patients with VSSs. Methods The authors retrospectively analyzed the status of tinnitus before and
after surgery in 242 patients with unilateral VSs who underwent surgery via the retrosigmoid lateral suboccipital approach. Results Of 242 patients, 171 (70.7%) complained of tinnitus before surgery; the symptom disappeared in 25.2%, improved in 33.3%, remained unchanged in 31.6%, and worsened in 9.9% of these cases after tumor removal. In the 171 patients with preoperative tinnitus, the cochlear nerve was resected in 85 (49.7%) and preserved in 86 (50.3%), but there was no significant difference in the incidence of postoperative tinnitus between these 2 groups (p = 0.293). In the 71 patients without preoperative tinnitus, the symptom developed postoperatively in 6 cases (8.5%). Among those without preoperative tinnitus, the cochlear nerve was resected in 45 cases (63.4%) and tinnitus appeared postoperatively in 3 (6.7%). The authors also analyzed the association between postoperative tinnitus and useful hearing preservation, but could not find any statistically significant association between the 2 factors (p = 0.153). Conclusions Tumor removal via the retrosigmoid lateral suboccipital approach may provide some chance for improvement of tinnitus in patients with VSs; however, neither cochlear nerve resection nor useful hearing preservation affects the postoperative development of tinnitus.

Tenotomy of the tensor tympani and stapedius tendons in Ménière’s disease.

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Tenotomy of the tensor tympani and stapedius tendons in Ménière’s disease. OBJECTIVE: In Ménière’s disease (MD), when patients have incapacitating vertigo that is resistant to drug treatment, an intratympanic gentamicin application (ITG) is often proposed. Recently, some authors suggested that tenotomy, sectioning of the tensor tympani and stapedius tendons, could be a promising treatment. We examined whether tenotomy (ST) has additional benefit, compared to ITG alone, with respect to tinnitus, vertigo, and quality of life. METHODOLOGY: We conducted a retrospective survey of the charts of 24 patients with MD who underwent ITG, or ITG plus ST. Baseline data and follow-up assessments were obtained, using the Ménière’s Disease Outcomes Questionnaire (MDOQ), the Dizziness Handicap Inventory (DHI), vertigo frequency per month, tinnitus visual analogue scale, and functional level. Failure was determined by the need for an additional procedure. RESULTS: ITG was performed on 15 patients, and 9 patients underwent ITG plus ST. The procedure was sufficient in 53% of the ITG group and in 22% of the ITG plus ST group. No significant difference was found between the two groups concerning MDOQ scores, DHI, functional level, vertigo frequency, and tinnitus. In the ITG group, we found a significant improvement in number of vertigo attacks and the tinnitus visual analogue scale. In the ITG plus ST group, there was a significant reduction in vertigo attacks, but not in tinnitus. CONCLUSION: This preliminary study suggests no additional benefit of stapedius and tensor tympani tenotomy in the treatment of Ménière’s disease patients.

Bilateral carotid endarterectomy as treatment of vascular pulsatile tinnitus.

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Atherosclerotic carotid artery disease (ACAD) is a rare but recognized cause of pulsatile tinnitus. Existing literature of reported cure for pulsatile tinnitus is reviewed. We found: (1) a male preponderance exists; (2) ipsilateral carotid endarterectomy (CEA) for tinnitus is 92% (12 of 13) effective; (3) proximal lesions lend themselves to CEA whereas distal lesions have been treated by stenting; (4) overall 68% (15 of 22) are cured by intervention; and (5) 89% (17 of 19) can expect immediate relief. We now present a case of bilateral pulsatile tinnitus relieved by bilateral carotid endarterectomy.
Clinical presentation and management of jugular foramen paraganglioma.

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OBJECTIVES: Jugular foramen paraganglioma is a locally invasive, benign tumor, which grow slowly and causes various symptoms such as pulsatile tinnitus and low cranial nerve palsy. Complete surgical resection is regarded as the ideal management of these tumors. The goal of this study is to identify the clinical characteristics and most effective surgical approach for jugular foramen paraganglioma.

METHODS: Retrospective analysis of 9 jugular foramen paraganglioma patients who underwent surgical resection between 1986 and 2005 was performed. Clinical records were reviewed for analysis of initial clinical symptoms and signs, audiological examinations, neurological deficits, radiological features, surgical approaches, extent of resection, treatment outcomes and complications.

RESULTS: Most common initial symptom was hoarseness, followed by pulsatile tinnitus. Seven out of 9 patients had at least one low cranial nerve palsy. Seven patients were classified as Fisch Type C tumor and remaining 2 as Fisch Type D tumor on radiologic examination. Total of 11 operations took place in 9 patients. Total resection was achieved in 6 cases, when partial resection was done in 3 cases. Two patients with partial resection received gamma knife radiosurgery (GKS), when remaining 1 case received both GKS and two times of revision operation. No mortality was encountered and there were few postoperative complications.

CONCLUSION: Neurologic examination of low cranial nerve palsy is crucial since most patients had at least one low cranial nerve palsy. All tumors were detected in advanced stage due to slow growing nature and lack of symptom. Angiography with embolization is crucial for successful tumor removal without massive bleeding. Infratemporal fossa approach can be considered as a safe, satisfactory approach for removal of jugular foramen paragangliomas. In tumors with intracranial extension, combined approach is recommended in that it provides better surgical view and can maintain the compliance of the patients.

Traumatic stapes fracture with rotation and subluxation into the vestibule and pneumolabyrinth.

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A 41-year-old man presented after forceful penetrating ear injury. He had incapacitating vestibular symptoms. Computed tomography revealed pneumolabyrinth with a fractured stapes that was >90 degrees rotated and subluxed into the vestibule, such that the crura and capitulum could be seen in the vestibule. Surgical repair reversed the vestibular symptoms, but there was persistent hearing loss. Stapes fractures are unusual and rarely associated with subluxation into the vestibule. When this does occur, there is usually simple footplate depression. This case demonstrates a rare stapes fracture with pneumolabyrinth and >90 degrees stapes rotation, then subluxation into the vestibule. Laryngoscope, 2009.

Endovascular management of dural arteriovenous fistulas of the transverse and sigmoid sinus in 150 patients.

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INTRODUCTION: This study aimed to evaluate the safety and efficiency of the endovascular treatment of transverse-sigmoid sinus dural arteriovenous fistulas (TS_dAVF). METHODS: A total of 150 consecutive patients and 348 procedures were evaluated. RESULTS: Pulsatile tinnitus (81%), headache (15%), and intracranial hemorrhage (10%) were the most frequent manifestations of the TS_dAVFs.
More than half of the affected sinuses were partially or completely thrombosed. Access-wise treatment was performed transarterial (n = 33), transvenous (n = 21), or a combination thereof (n = 96). A mean of 2.4 procedures per patient was required. Immediate postprocedural occlusion rate after transarterial embolization was 30% only. Transvenous treatment alone resulted in an early occlusion rate of 81%, with delayed complete obliteration of half of the remaining fistulas. After combined transarterial/transvenous treatment, the angiographic cure rate was 54%. At follow-up, 88% of patients with residual shunt after the treatment showed complete occlusion. The cumulative complication rate was 9% (n = 13), with minor adverse events in ten patients (7%) and major complications in three patients (2%).

CONCLUSION: Transvenous coil occlusion of the sinus segment with the adjacent dAVF site, eventually combined with transarterial occlusion of supplying arteries, is a very effective and well-tolerated treatment method. In selected patients, variations of these methods (e.g., sinus stenting, compartmental sinus occlusion) can be useful.

XI Holistics

The root and development of otorhinolaryngology in traditional Chinese medicine.
Eur Arch Otorhinolaryngol. 2009 Jul 14.
Yap L, Pothula VB, Warner J, Akhtar S, Yates E.
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There is an increasing trend in society to look beyond conventional medicine to find answers to problems in health. Traditional Chinese medicine (TCM) is one of the most popular alternative, complementary therapies worldwide. It is becoming a popular alternative in otorhinolaryngology where its use in the treatment of sinusitis, tinnitus, deafness and Meniere’s disease is growing. Despite the general awareness of TCM, the literature relating specifically to otorhinolaryngology is relatively scarce. In this review, we have traced the origin and development of otorhinolaryngology with respect to TCM and have provided a few interesting insights into otorhinolaryngology, as it used to be practised. Archaeological sources have shown that diseases affecting the ear, nose and throat were of medical concern as early as the 18th century BC. The first practising otorhinolaryngologist can be traced back to the 5th century BC. Acupuncture, moxibustion, herbal therapy and massage were amongst his treatments. Otorhinolaryngology was recognised as a major specialty when formal medical education began in the 7th century AD. Therapeutic measures since then expanded to include exercise, food therapy and surgery. References to using oesophageal speech as a substitute voice generator, the use of copper wire to excise nasal polyps, procedures for removal of sharp foreign bodies in the oropharynx, repair of lacerated trachea and treatment of cancer of lips can be found in historical notes. In conclusion, from its primitive roots, TCM has developed into a distinct branch of health care system in China today that works alongside Western medicine.

The NGF point-injection for treatment of the sound-perceiving nerve deafness and tinnitus in 68 cases.
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OBJECTIVE: To observe the therapeutic effects of the point-injection with nerve growth factor (NGF) for the sound-perceiving nerve deafness and tinnitus. METHODS: The 140 cases in this series were randomly divided into a treatment group of 68 cases treated by NGF injection at the points of Yifeng (TE 17) and Wangu (GB 12), and a control group of 72 cases orally taking Xibiling and adenosine triphosphate (ATP) and intramuscular injection with VB1 and VB12. RESULTS: The total effective rate was 78.6% in the treatment group and 31.8% in the control group, with significant difference between the two groups (P<0.05). CONCLUSION: For treating nervous deafness and tinnitus, NGF point-injection may show good therapeutic effects, but inversely proportional to the illness course, age and the extent of hypoacusis.
Tinnitus: characteristics, causes, mechanisms, and treatments.

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Tinnitus—The perception of sound in the absence of an actual external sound—represents a symptom of an underlying condition rather than a single disease. Several theories have been proposed to explain the mechanisms underlying tinnitus. Tinnitus generators are theoretically located in the auditory pathway, and such generators and various mechanisms occurring in the peripheral auditory system have been explained in terms of spontaneous otoacoustic emissions, edge theory, and discordant theory. Those present in the central auditory system have been explained in terms of the dorsal cochlear nucleus, the auditory plasticity theory, the crosstalk theory, the somatosensory system, and the limbic and autonomic nervous systems. Treatments for tinnitus include pharmacotherapy, cognitive and behavioral therapy, sound therapy, music therapy, tinnitus retraining therapy, massage and stretching, and electrical suppression. This paper reviews the characteristics, causes, mechanisms, and treatments of tinnitus.

Chronic tinnitus: a grading management mode study

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OBJECTIVE: To probe into grading management mode for chronic tinnitus victims, so as to improve the cost-effectiveness rate of tinnitus treatment. METHODS: According to the severity of patient's own feeling and the therapy demand, the authors managed 587 of chronic tinnitus victims using a progressive methods: Level 1 was primary evaluation, counseling and treatment for tinnitus victims, then determined if the victim require further clinical intervention. Level 2 was educational counseling about the knowledge of tinnitus. Level 3 was further evaluation for hearing function and the severity of tinnitus. Than the authors made and put in practice an individual integrative treatment project for every victim according to the assessment results. RESULTS: 75% (441/587) of the chronic tinnitus victims needed only educational counseling which can free them from the mystification and dread of tinnitus, the counseling helped them get habituation of tinnitus; the rest 25% (146/587) needed long-term integrative clinical treatment. CONCLUSION: Effective grading management can hold the tinnitus severity level and the treatment desirability from the victims rapidly and exactly, then provided them multiple modalities treatment from counseling to long-term integrative therapy. The grading management mode improved the cost-effectiveness rate of tinnitus treatment.

Ménière's disease.

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Ménière’s disease affects about 1% of the population. Typically it presents as episodic vertigo, fluctuating hearing loss, tinnitus and aural fullness. The history and physical examination are critical in making the diagnosis. Laboratory tests are useful in tailoring and following up patients. Treatment options are limited and usually targeted towards reducing endolymphatic hydrops to stabilise the hearing loss and reduce the vertiginous episodes.
Menière’s disease is recognized as the idiopathic form of recurrent inner ear disease with the trias of hearing loss, tinnitus and vertigo with aural fullness and Menière’s syndrome as the non-idiopathic form. Subentities with unknown pathogenesis are Lermoyez’ s syndrome and Tumarkin crises. A common pathogenetic factor is the disturbance of endolymphatic and perilymphatic osmotic and hydrostatic pressure due to defined etiologies or to idiopathic attacks. Etiologies of Menière's syndrome can be pathologic middle ear pressure, anomalies of the vestibular and cochlear aqueducts, round window topography, patency of the ductus peruniens and the utriculo-endolymphatic valve. Indications for treatment are assessed according to the AAO-HNS guidelines and the neurotological function tests and dizziness inventories. Betahistine is recommended as first choice medical treatment as on-label or high dosage administration. In case of medical treatment failure and if hearing is worth saving, endolymphatic shunt surgery (ELS) is the first choice. If deafferentiation of the labyrinth is needed vestibular neurectomy (VE) should be performed. Local gentamicine administration has good long-term results but macula function can often recover and hearing is often deteriorated. Future aspects for the treatment are new experimental results with gene transfer to vestibular hair cells.

INTRODUCTION AND DEVELOPMENT: Sensory systems show a topographic representation of the sensory epithelium in the central nervous system. In the auditory system this representation originates tonotopic maps. For the last four decades these changes in tonotopic maps have been widely studied either after peripheral mechanical lesions or by exposing animals to an augmented acoustic environment. These sensory manipulations induce plastic reorganizations in the tonotopic map of the auditory cortex. By contrast, acoustic trauma does not seem to induce functional plasticity at subcortical nuclei. Mechanisms that generate these changes differ in their molecular basis and temporal course and we can distinguish two different mechanisms: those involving an active reorganization process, and those that show a simple reflection of the loss of peripheral afferences. Only the former involve a genuine process of plastic reorganization. Neuronal plasticity is critical for the normal development and function of the adult auditory system, as well as for the rehabilitation needed after the implantation of auditory prostheses. However, development of plasticity can also generate abnormal sensation-like tinnitus. Recently, a new concept in neurobiology so-called ‘neuronal stability’ has emerged and its implications and conceptual basis could help to improve the treatments of hearing loss. CONCLUSION: A combination of neuronal plasticity and stability is suggested as a powerful and promising future strategy in the design of new treatments of hearing loss.
XIII Others

[Expert assessment of tinnitus in statutory accident insurance]
[Article in German]

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Tinnitus is defined as hearing sensation without external noise source. The aetiology contains also occupational causes such as noise industrial pollution and inner ear trauma, nevertheless the origin of tinnitus is vastly unexplained. For the expert assessment in the public insurance a step-by-step procedure is recommended: Is there a tinnitus? Was the accused cause able to provoke tinnitus? How profound is the insured person hindered in his individual work ability by the tinnitus and potential psycho vegetative reactions? In this publication hints for tinnitus-matching and for expert opinion related questions are given: is there a noise-caused tinnitus in the low frequencies? Is it possible that a noise-induced tinnitus worsens after retirement? Can stress be a potential candidate to evoke tinnitus? Under which circumstances a psychiatric assessment can be necessary? In the assessment of tinnitus crucial differences between public accident insurance, civil right, public health and handicap right are explained.

Tinnitus as a measure of salicylate toxicity in the overdose setting.

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INTRODUCTION: The development of tinnitus and/or hearing loss (THL) in patients receiving chronic salicylate therapy has been demonstrated. However, to date, little scientific data validates this relationship in the large single overdose setting. OBJECTIVE: To correlate salicylate levels in patients with the subjective complaint of THL, following an acute salicylate overdose. METHODS: A retrospective chart review of cases of acute salicylate toxicity and THL reported to the Illinois Poison Control Center (IPC) from 2001-2002 was performed. Data abstracted included age, gender, ingestion time, salicylate levels, and arterial blood gases. RESULTS: Ninety-nine cases of THL were reviewed and analyzed with mean age of 23.7 years (SD: 10.9), 30.3% male, and 82.2% intentional overdoses. The average dose ingested was 20.0 grams (SD:20.2) and the mean time from ingestion to medical care was 12.4 hours (SD: 11.1). The mean initial ASA level was 48.3 mg/dl (SD: 16.4) with 86.9% having initial level >/=30mg/dl and 40.4% >/=50 mg/dl. 85.9% of cases presented to the hospital with their ASA level at or past peak. The mean pH was 7.45, pO2 = 108, pCO2 = 28.0, and HCO3 = 19.9. CONCLUSION: In this limited study, 85.9% of patients presenting with tinnitus and/or hearing loss following a single salicylate ingestion had initial salicylate levels at or past their peak and 86.9% were in the toxic range.

Tinnitus as a warning for preventing vasovagal syncope.

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It has been widely outlined by our group the possibility that a sufferance of the inner ear can take place as a consequence of hemodynamic imbalance which could affect young and healthy people and recognize a merely functional origin. As reported in previous papers, an altered reaction of the autonomic nervous system could actually jeopardize the labyrinthine perfusion even in absence of other damages. From this standpoint, the hypothesis that a hyperactivity of the vagal response to an acute sympathetic drive may result in an inner ear sufferance deserves to be explored. A mechanism which appears to fit to this model is represented by the Bezold-Jarisch reflex (BJR), which is considered to be responsible for vasovagal syncope and is characterized by a dynamic reasonably compatible with our findings. According to these premises, especially considering that the inner ear has a less active protective mechanism against ischemia as compared to brain, in predisposed subjects tinnitus, when considered
as an initial symptom of inner ear hypoperfusion, can represent a warning able to prevent the lack of consciousness related to the syncope.

**Patient-centered tinnitus management tool: a clinical audit.**

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PURPOSE: To evaluate the impact of an educational poster describing treatment options available to patients experiencing tinnitus. METHOD: A patient-centered tinnitus management tool (PCTMT) was developed in the form of an educational poster that encouraged patients to decide how they wanted to deal with their tinnitus from the following options: (a) ignore the tinnitus and forget about it, (b) use a sound generator, (c) undertake tinnitus counseling with an expert, or (d) deal with the tinnitus using hearing aids (in the case of tinnitus and hearing loss). Fifty-five patients who were referred to the audiology department of a London hospital from the ENT department for tinnitus counseling were asked to read the PCTMT and to choose the option(s) that suited them the best. RESULTS: Forty-two percent of the patients wished to undertake counseling, 9% decided to try to ignore their tinnitus without help, 26% wanted to deal with their tinnitus with the help of a sound generator, and 24% decided to use hearing aids. CONCLUSIONS: The PCTMT reduced the number of patients who would otherwise have been referred for tinnitus counseling by 58%. This reduced the length of the waiting list and increased the time available for counseling of those patients who wanted it.

**Neurological Problems of Famous Musicians: The Classical Genre.**

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Deputy Joint Program Executive Officer, Medical Systems Joint Program Executive Office for Chemical/Biological Defense.

Neurological histories of great musicians allow for a unique perspective on music physiology. Bedrich Smetana’s autobiographical string quartet ends with the musical equivalent of tinnitus in the fourth movement, rendering the youthful and passionate themes of earlier movements moot as the piece ends depicting his ultimately fatal disease, neurosyphilis. Dmitri Shostakovich survived the censorship of Joseph Stalin’s apparatchiks but suffered a prolonged form of paralysis attributable to slowly progressive motor neuron disease, although the viola sonata he wrote on his deathbed has become standard repertoire. Glenn Gould was a hypochondriacal pianist with obsessive-compulsive disorder and suspected Asperger syndrome. Vissarion Shebalin and (Ira) Randall Thompson had strokes followed by aphasia without amusia. Domenico Scarlatti provides an example of how even great composers must alter their technical expectations depending upon the skills and body habitus of their chief patrons. The focal dystonia afflicting Leon Fleisher and Gary Graffman catalyzed the discipline of performing arts medicine.

**XIV Case Reports**

**An unusual middle-ear mass.**

Muller M, Zammit-Maempel I, Hill J, Wilkins B.
Department of Radiology, Freeman Hospital, Newcastle upon Tyne, UK.

Objective: We describe a case of endolymphatic sac tumour confined to the middle ear, which radiologically mimicked a glomus tympanicum, in a 58-year-old woman with tinnitus. Case report: A 58-year-old woman presented with a one-year history of right-sided tinnitus. The clinical, radiological and surgical features were felt to be in keeping with a glomus tympanicum. However, the histopathological picture was that of a low grade papillary carcinoma of the endolymphatic sac, i.e. an endolymphatic...
sac tumour. Conclusion: Endolymphatic sac tumours are classically locally aggressive and centred around the petrous temporal bone. Further growth results in complete replacement of the mastoid and petrous pyramid by tumour. To the best of our knowledge, there have been no previous reports of an endolymphatic sac tumour located solely within the hypo- and epitympanum of the middle ear.

Serial retinal fluorescein angiography and immune therapy in Susac's Syndrome.

Mallam B, Damato EM, Scolding NJ, Bailey C.
Neurology Department, University of Bristol Institute of Clinical Neurosciences, Frenchay Hospital, Bristol BS16 1LE, United Kingdom.

We report a patient with Susac's disease presenting classically in a young female with an encephalopathy and visual disturbance with later deafness and tinnitus. Her encephalopathy settled, but subsequent serial fluorescein angiograms allowed sensitive monitoring of continuing sub-clinical disease activity, and provide evidence of a clear therapeutic response to immune suppression with tacrolimus (but not steroids alone) - and of a lack of efficacy of nimodipine and aspirin. We believe this single case study has both pathogenetic and useful practical implications: the apparently favourable response to immunosuppression lends support to the hypothesis that Susac's Syndrome is an immune-mediated disease; while the presence during symptomatic clinical remission of sporadic, multi-focal episodes of hyper-fluorescence, suggestive of breakthrough vasculopathy despite treatment, underlines the fact that the natural history of this rare condition is still not fully understood. Fluorescein angiography is proposed as a sensitive and important approach to the monitoring of sub-clinical disease activity, and so optimising immune suppressive treatment.

Parallel transverse-sigmoid sinus harboring dural arteriovenous malformation. How to differentiate the pathological and normal sinus in order to treat and preserve patency and function.

de Paula Lucas C, Prandini MN, Spelle L, Piotin M, Mounayer C, Moret J.
Department of Neurosurgery of the Federal University of São Paulo, São Paulo, Brazil, cesar.lucas@uol.com.br.

An unusual case of dural arteriovenous malformation (DAVM) harboring a parallel transverse-sigmoid sinus (TSS) is presented. The patient had a 2-year history of left-sided pulsatile tinnitus in the left ear refractory to medical management. Angiography demonstrated a DAVM involving the left TSS. Super-selective transvenous dural sinus occlusion of the DAVM situated at the pathological compartment of the TSS provided cure. We were able to spare the normal compartment providing anatomical venous drainage from this system.

Pulsatile tinnitus from reversal of flow in an aberrant occipital artery: resolved after carotid artery stenting.

Cowley PO, Jones R, Tuch P, McAuliffe W.
Department of Diagnostic and Therapeutic Neuroradiology and Interventional Services of Western Australia, Sir Charles Gairdner and Royal Perth Hospitals, Perth, WA, Australia. pedrocowley@gmail.com

Carotid artery stent placement, performed for correction of an asymptomatic severe stenosis, leads to the resolution of persistent and troublesome pulsatile tinnitus. Tinnitus has been reported as a consequence of severe carotid stenoses on previous occasions. This case highlights how an aberrant occipital artery originating above a carotid artery stenosis can result in flow reversal and be a mechanism by which tinnitus may develop.
Coexistence of acute hearing loss with retinal artery occlusion and encephalopathy.

Wimmer E, Kramer MF, Bergmann C, Reiniger I, Harrèus U.
Department of Otorhinolaryngology, Head and Neck Surgery, Ludwig-Maximilians-University Munich, Germany. eva.wimmer@med.uni-muenchen.de

We characterize 2 cases with sensorineural hearing loss and ophthalmologic findings. The clinicopathologic features revealed diagnosis of Susac's syndrome, a rare microangiopathy with cochlea, retinal, and brain affection. Diagnosis may be difficult because most specialists are not familiar with this angiopathy. However, the characteristic symptoms can mimic different pathologies, which may result in attention of radiologists, ophthalmologists, neurologists and otolaryngologists. In this report, we present 2 women with Susac's syndrome unveiled by audiometry, magnetic resonance imaging of the brain, and ophthalmologic findings. The course of the illness and a review of literature are presented.

Gabapentin responsive audiovestibular paroxysmia.

Russell D, Baloh RW.
Jefferson Medical College, 1020 Walnut Street, Philadelphia, PA 19107-5587, USA. douglas.russell@jefferson.edu

Trigeminal neuralgia and hemifacial spasm are well-documented vascular compression syndromes involving the 5th and 7th cranial nerves. Drugs that stabilize the irritated nerves and vascular decompression surgery are accepted treatments. By contrast, the diagnosis and treatment of a comparable syndrome involving the 8th cranial nerve is controversial. We describe two patients with brief, spontaneous, recurrent attacks of tinnitus and vertigo that responded to low dose gabapentin and we argue that this clinical presentation represents the prototypical 8th nerve vascular compression syndrome.

Middle Ear Adenoma: A Challenging Diagnosis.

Zan E, Limb CJ, Koehler JF, Yousem DM.
Russell H. Morgan Department of Radiology and Radiological Science, and Department of Otolaryngology-Head and Neck Surgery, The Johns Hopkins Hospital, Baltimore, Md; and Division of Surgical Pathology, Johns Hopkins Medical Institutions, Baltimore, Md.

SUMMARY: Middle ear adenomas are rare benign tumors, which can easily be mistaken for other conditions radiologically. They derive from the middle ear mucosa. We report the case of a 48-year-old man with a history of decreased left-sided hearing and intermittent pulsatile tinnitus. High-resolution CT of the temporal bones revealed a well-defined left middle ear soft-tissue attenuation abutting the head of the malleus. Surgical excision revealed a middle ear adenoma.
Clinical Trials
Source: clinicaltrials.gov (23 July 2009)

Cognitive Behavioral Therapy (CBT) for Tinnitus

<table>
<thead>
<tr>
<th>Current status</th>
<th>currently recruiting participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsors and collaborators</td>
<td>Department of Veterans Affairs, Yale University</td>
</tr>
<tr>
<td>Information provided by</td>
<td>Department of Veterans Affairs</td>
</tr>
<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT00724152</td>
</tr>
</tbody>
</table>

**Purpose**

This study examines how useful it is to teach veterans coping skills for dealing with tinnitus, also called ringing in the ears. A psychological intervention, cognitive-behavioral therapy, will be used to teach coping skills even though tinnitus is not a psychological disorder. Participants will be assigned to one of two groups for the duration of the study and will not know which group they are in until the end of the study. One group will receive education about tinnitus. The other group will receive education about tinnitus plus additional ways to cope with problems associated with tinnitus such as sleep disturbance and frustration. Several questionnaires will be filled out by veterans interested in participating in the study.

Participants will be selected to participate if their tinnitus is severe and they were exposed to loud sound. Some veterans may not be eligible to participate if they have additional health conditions. About 66 veterans will be enrolled in the study. If selected to participate in the study, veterans will attend six weekly group meetings. Participants will then be asked to come back 8 weeks after the last group to answer more questions about their tinnitus and health. It is predicted that participants who are assigned to the cognitive behavioral therapy group will report a greater reduction in tinnitus severity.

**Condition(s)**

Cognitive Behavior Therapy
Health Education

**Phase**

I
II

**Interventions**

Behavioral: Cognitive Behavioral Therapy
Other: Tinnitus Education

**Study type and design**

Interventional; Treatment, Randomized, Single Blind (Subject), Active Control, Parallel Assignment, Efficacy Study

**Official title**

Cognitive-Behavioral Therapy for Tinnitus

**Detailed Description**

The objectives of this study are to (1) develop a novel, integrative, psychological intervention, specifically cognitive-behavioral therapy (CBT), for the treatment of tinnitus among veterans who have past exposure to loud noise, and (2) accrue preliminary data examining the efficacy of the approach relative to a standard care with education (ED) control condition. Tinnitus was the most common new individual service-connected disability in fiscal year 2006. Treatments for tinnitus are few and no cure exists. This pilot study will examine the feasibility and efficacy of providing individualized (CBT) for veterans with bothersome tinnitus. Sixty-six veterans will be recruited and randomly...
selected to one of two conditions: the treatment condition (CBT) or the (ED) control condition. A two-group design with two continuous dependent variables will be used to compare improvements between the control group (ED) and the experimental group (CBT). Covariates will include age and number of months with tinnitus. It is hypothesized that the CBT group will improve greater (get lower scores on the THI and TRQ than the ED group) though not to the level of statistical significance. A CBT manual and an ED manual will be developed for this study. Subjects will be eligible for the study if their tinnitus was likely caused by noise exposure, their tinnitus is chronic (> 6 months), tinnitus is a major health concern for them, and participants are able to commit to a 6-week course of treatment at the West Haven location of VACHS. Subjects will be veterans blinded to the treatment group to which they are assigned. Potential subjects will respond to five assessment measures to determine inclusion in the study: (1) Tinnitus-Impact Screening Interview (TISI), (2) Semi-Structured Clinical Interview for Tinnitus (SSCIT), (3) Structured Clinical Interview for Diagnosis, abbreviated - Interview/Non-patient (SCIDa-I/NP), (4) Tinnitus Handicap Inventory (THI), and (5) Tinnitus Reaction Questionnaire (TRQ). Subjects will attend six group meetings and undergo evaluations before three group meetings and after all six group meetings. The THI and TRQ will serve as the primary outcome measures and will be administered before the first group meeting, after the sixth group meeting at 8 weeks post-treatment follow-up. Results of this pilot project will be used to inform the design and methods of a future rigorous randomized controlled clinical trial of CBT for tinnitus.

Arms

1: Active Comparator
Participants randomly assigned to this control group will receive six weeks of tinnitus education

2: Experimental
Participants randomly assigned to this experimental group will receive six weeks of tinnitus education plus cognitive behavioral therapy.

Assigned Interventions

1. Other: Tinnitus Education
Tinnitus education will include causes, treatments, current research, epidemiological information, basic anatomy of the ear and brain, and support resources.

2. Behavioral: Cognitive Behavioral Therapy
Cognitive behavioral therapy for tinnitus participants will address cognitive and behavioral skills targeting the management of tinnitus and the negative impacts of tinnitus. Long-term self-efficacy and self-sufficiency will be used emphasized. The major components of CBT for tinnitus include identification of individual responses and beliefs about tinnitus and hearing loss, re-conceptualization of the tinnitus experience as one in which the patient has personal control, presentation of skills to modify cognitions (such as negative appraisals) and change behaviors (such as avoidance of social activities), and reinforcement of skills via goals setting, homework and activities. Tinnitus education and skills related to attention control, sleep hygiene and relaxation training such as imagery techniques will be provided. Other: Tinnitus Education
Tinnitus education will include causes, treatments, current research, epidemiological information, basic anatomy of the ear and brain, and support resources.
Tinnitus Handicap Inventory (THI) [Time Frame: Eligibility, pre-treatment, post-treatment, 8-weeks post-treatment] [Designated as safety issue: No]

Tinnitus Reaction Questionnaire (TRQ) [Time Frame: Eligibility, pre-treatment, post-treatment, 8-weeks post-treatment] [Designated as safety issue: No]

Expected total Enrollment 66

Study start February 2009

Repetitive Transcranial Magnetic Stimulation (rTMS) for Tinnitus

Current status currently recruiting participants

Sponsors and collaborators UMC Utrecht

Information provided by UMC Utrecht

ClinicalTrials.gov Identifier NCT00668720

Purpose Tinnitus is a phantom auditory perception of meaningless sound, meaning that there is registration of sound in the absence of an external or internal acoustic stimulus. It is a common problem (prevalence 7-19%) which may interfere with the ability to lead a normal life. Unfortunately, it is a very difficult symptom to treat because there are hardly any therapeutic options for the cause of tinnitus. Most therapies focus on alleviating the condition rather than treating the cause. Tinnitus is thought to be generated in the brain, as a result of functional reorganization of auditory neural pathways and tonotopic maps in the central auditory system, following damage to the peripheral auditory system. Repetitive Transcranial magnetic stimulation (rTMS) is a therapy, based on this concept of reorganization in the auditory cortex. It uses a pulsed magnetic field to disrupt the neural circuit and to thereby (temporarily) excite or inhibit certain brain areas, leading to the suppression of tinnitus.

Condition(s) Tinnitus

Interventions Device: transcranial magnetic stimulation (Magstim rapid2) Device: sham stimulation

Study type and design Interventional; Treatment, Randomized, Double Blind (Subject, Caregiver, Outcomes Assessor), Placebo Control, Parallel Assignment, Efficacy Study

Official title Effectiveness of Repetitive Transcranial Magnetic Stimulation (rTMS) Treatment in Patients With Chronic Tinnitus

Arms 1: Experimental 2: Sham Comparator
| Assigned Interventions | 1. Device: transcranial magnetic stimulation (Magstim rapid2) Neuronavigated rTMS will be applied bilaterally to the auditory cortices, which will be identified through a structural MRI scan. Stimulation will be performed with 1 Hz frequency and an intensity of 110% motor threshold for 2000 stimuli (32 minutes) on each side, on five subsequent days.  
2. Device: sham stimulation The official sham stimulator for the magstim rapid2 will be used. Sham stimulation will follow the same placement protocol and will also last 2x32 minutes on five subsequent days |
| Primary Outcomes | Tinnitus severity with the Tinnitus Questionnaire [Time Frame: after treatment, 1 week, 1, 3 and 6 months] [Designated as safety issue: No] |
| Secondary Outcomes | • Tinnitus Handicap Inventory [Time Frame: after treatment, 1 week, 1, 3 and 6 months] [Designated as safety issue: No]  
• Beck Depression Inventory [Time Frame: after treatment, 1 week, 1, 3 and 6 months] [Designated as safety issue: No]  
• State Trait Anxiety Index [Time Frame: after treatment, 1 week, 1, 3 and 6 months] [Designated as safety issue: No]  
• Visual Analog Scales on burden, loudness, pitch, presence, and variability of tinnitus and specific problems. [Time Frame: for the first three months daily and for the second three months monthly] [Designated as safety issue: No]  
• Audiometry and tinnitus analysis (character match, pitch match, loudness match, minimal masking level, residual inhibition) [Time Frame: 1 week after treatment and after 3 and 6 months] [Designated as safety issue: No] |
| Expected total Enrollment | 52 |
| Study start | April 2008 |
| Expected primary completion date | December 2008 (Final data collection date for primary outcome measure) |
| Participants (age) | 18 Years and older |
| Gender | Both |
| Accepts health volunteers | No |
| Eligibility Inclusion Criteria | • Chronic, non fluctuating, tinnitus, demonstrated by means of the diagnostic Protocol Tinnitus UMCU, of at least two months duration.  
• Age ≥18 years |
| Eligibility Exclusion Criteria | • Treatable cause of the tinnitus  
• Use of anticonvulsant medication or other psychotherapeutic drugs  
• History of epilepsy or family members with epilepsy  
• Presence of active migraine  
• Presence of psychiatric, severe internal or heart diseases or other neurologic diseases besides epilepsy |
| **Contact** | Carlijn EL Hoekstra, MD, phone +31-88-755-3606, c.e.l.hoekstra@umcutrecht.nl  
| | Bert A van Zanten, AuD, phone +31-88-755-3702, g.a.vanzanten@umcutrecht.nl |
| **Locations** | University Medical Center Utrecht, Recruiting, Utrecht, Netherlands, 3584 CX |
| **Study chairs or principal investigators** | Carlijn EL Hoekstra, MD  
| | Bert A van Zanten, AuD, Dept. of Otorhinolaryngology, University Medical Center Utrecht |
| **Study ID Numbers** | rTMS_tinnitus_Utrecht |
| **Last Updated** | April 25, 2008 |
| **Record first received** | April 25, 2008 |
| **ClinicalTrials.gov Identifier** | NCT00668720 |
| **Health Authority** | Netherlands: The Central Committee on Research Involving Human Subjects (CCMO) |

**Cognitive Behavioral Therapy (CBT) for Tinnitus**

| **Current status** | not yet open for participant recruitment |
| **Sponsors and collaborators** | Department of Veterans Affairs  
| | Yale University |
| **Information provided by** | Department of Veterans Affairs |
| **ClinicalTrials.gov Identifier** | NCT00724152 |
| **Purpose** | This study examines how useful it is to teach veterans coping skills for dealing with tinnitus, also called ringing in the ears. A psychological intervention, cognitive-behavioral therapy, will be used to teach coping skills even though tinnitus is not a psychological disorder. Participants will be assigned to one of two groups for the duration of the study and will not know which group they are in until the end of the study. One group will receive education about tinnitus. The other group will receive education about tinnitus plus additional ways to cope with problems associated with tinnitus such as sleep disturbance and frustration. Several questionnaires will be filled out by veterans interested in participating in the study. Participants will be selected to participate if their tinnitus is severe and they were exposed to loud sound. Some veterans may not be eligible to participate if they have additional health conditions. About 66 veterans will be enrolled in the study. If selected to participate in the study, veterans will attend six weekly group meetings. Participants will then be asked to come back 8 weeks after the last group to answer more questions about their |
tinnitus and health. It is predicted that participants who are assigned to the cognitive behavioral therapy group will report a greater reduction in tinnitus severity.

| Condition(s)          | 1. Cognitive Behavior Therapy  
<table>
<thead>
<tr>
<th></th>
<th>2. Health Education</th>
</tr>
</thead>
</table>
| Interventions         | 1. Behavioral: Cognitive Behavioral Therapy  
|                       | 2. Other: Tinnitus Education  |
| Phase                 | 1. Phase I                     |
|                       | 2. Phase II                    |
| Study type and design | Interventional; Treatment, Randomized, Single Blind (Subject), Active Control, Parallel Assignment, Efficacy Study |
| Official title        | Cognitive-Behavioral Therapy for Tinnitus |
| Arms                  | 1: Active Comparator          |
|                       | Participants randomly assigned to this control group will receive six weeks of tinnitus education.  |
|                       | 2: Experimental               |
|                       | Participants randomly assigned to this experimental group will receive six weeks of tinnitus education plus cognitive behavioral therapy.  |

| Assigned Interventions | 1. Other: Tinnitus Education  |
|                        | Tinnitus education will include causes, treatments, current research, epidemiological information, basic anatomy of the ear and brain, and support resources.  |
|                        | 2. Behavioral: Cognitive Behavioral Therapy  |
|                        | Cognitive behavioral therapy for tinnitus participants will address cognitive and behavioral skills targeting the management of tinnitus and the negative impacts of tinnitus. Long-term self-efficacy and self-sufficiency will be used emphasized. The major components of CBT for tinnitus include identification of individual responses and beliefs about tinnitus and hearing loss, re-conceptualization of the tinnitus experience as one in which the patient has personal control, presentation of skills to modify cognitions (such as negative appraisals) and change behaviors (such as avoidance of social activities), and reinforcement of skills via goals setting, homework and activities. Tinnitus education and skills related to attention control, sleep hygiene and relaxation training such as imagery techniques will be provided.  |
|                        | Other: Tinnitus Education  |
|                        | Tinnitus education will include causes, treatments, current research, epidemiological information, basic anatomy of the ear and brain, and support resources.  |

| Detailed Description | The objectives of this study are to (1) develop a novel, integrative, psychological intervention, specifically cognitive-behavioral therapy (CBT), for the treatment of tinnitus among veterans who have past exposure to loud noise, and (2) accrue preliminary data examining the efficacy of the approach relative to a standard care with education (ED) control condition. Tinnitus was the most common new individual service-connected disability in fiscal year 2006. Treatments for tinnitus are few and no cure exists. This pilot study will examine the feasibility and efficacy of providing individualized (CBT) for veterans with bothersome tinnitus. Sixty-six veterans will be recruited and randomly selected to one of two conditions; the treatment condition (CBT) or |
the (ED) control condition. A two-group design with two continuous dependent variables will be used to compare improvements between the control group (ED) and the experimental group (CBT). Covariates will include age and number of months with tinnitus. It is hypothesized that the CBT group will improve greater (get lower scores on the THI and TRQ than the ED group) though not to the level of statistical significance. A CBT manual and an ED manual will be developed for this study. Subjects will be eligible for the study if their tinnitus was likely caused by noise exposure, their tinnitus is chronic (> 6 months), tinnitus is a major health concern for them, and participants are able to commit to a 6-week course of treatment at the West Haven location of VACHS. Subjects will be veterans blinded to the treatment group to which they are assigned. Potential subjects will respond to five assessment measures to determine inclusion in the study: (1) Tinnitus-Impact Screening Interview (TISI), (2) Semi-Structured Clinical Interview for Tinnitus (SSCIT), (3) Structured Clinical Interview for Diagnosis, abbreviated - Interview/Non-patient (SCIDa-I/NP), (4) Tinnitus Handicap Inventory (THI), and (5) Tinnitus Reaction Questionnaire (TRQ). Subjects will attend six group meetings and undergo evaluations before three group meetings and after all six group meetings. The THI and TRQ will serve as the primary outcome measures and will be administered before the first group meeting, after the sixth group meeting at 8 weeks post-treatment follow-up. Results of this pilot project will be used to inform the design and methods of a future rigorous randomized controlled clinical trial of CBT for tinnitus.

<table>
<thead>
<tr>
<th>Primary Outcomes</th>
<th>Tinnitus Handicap Inventory (THI) [Time Frame: Eligibility, pre-treatment, post-treatment, 8-weeks post-treatment] [Designated as safety issue: No]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary Outcomes</td>
<td>Tinnitus Reaction Questionnaire (TRQ) [Time Frame: Eligibility, pre-treatment, post-treatment, 8-weeks post-treatment] [Designated as safety issue: No]</td>
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<tr>
<td>Expected total Enrollment</td>
<td>66</td>
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<tr>
<td>Study start</td>
<td>November 2008</td>
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<tr>
<td>Expected study completion date</td>
<td>September 2009</td>
</tr>
<tr>
<td>Expected primary completion date</td>
<td>July 2009 (Final data collection date for primary outcome measure)</td>
</tr>
<tr>
<td>Participants (age)</td>
<td>18 Years and older</td>
</tr>
<tr>
<td>Gender</td>
<td>Both</td>
</tr>
<tr>
<td>Accepts health volunteers</td>
<td>No</td>
</tr>
<tr>
<td>Eligibility Inclusion Criteria</td>
<td>All subjects will be veterans who are currently receiving care at VACHS. Subjects must be interested in participating in the study and have moderate to severe, chronic (&gt;6 months) tinnitus. Following a brief assessment of tinnitus severity by the project coordinator, the research otologist and research audiologist will conduct tinnitus and audiological evaluations to determine subject eligibility. The most likely etiology of subjects’ tinnitus must be noise exposure to be included in the study and all eligible subjects will report having been exposed to loud sound some time in their lives. Subjects must indicate that</td>
</tr>
</tbody>
</table>
they are motivated to comply with treatment and able to commit to a 6-week course of treatment, follow-up, and study participation by continuing to reside nearby. Subjects must have stable, permanent housing and transportation means for follow-up appointments. Tinnitus will be a significant health concern for all subjects. Women and minorities will be recruited.

<table>
<thead>
<tr>
<th>Eligibility Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects will respond to five assessment measures to determine exclusion from the study.</td>
</tr>
<tr>
<td>1. Tinnitus-Impact Screening Interview (TISI): Those who score 4 or lower will be excluded from the study.</td>
</tr>
<tr>
<td>2. Semi-Structured Clinical Interview for Tinnitus: The exclusionary criteria described below will be assessed using this measure.</td>
</tr>
<tr>
<td>3. Structured Clinical Interview for Diagnosis, abbreviated - Interview Non-patient (SCIDa-I/NP): If there is any indication of psychosis on this measure, the subject will be excluded from the study.</td>
</tr>
<tr>
<td>4. Tinnitus Handicap Inventory (THI): Subjects with scores of 19 or lower will be excluded.</td>
</tr>
<tr>
<td>5. Tinnitus Reaction Questionnaire (TRQ): Subjects who score 16 or lower on this measure will be excluded from the study.</td>
</tr>
</tbody>
</table>

Subjects who are undergoing litigation or legal matters related to auditory disorders will be excluded from the study.

Subjects must never have previously received psychological treatment for their tinnitus.

Subjects who report having a history of traumatic brain injury (TBI) with loss of consciousness (LOC) will be excluded from the study.

Subjects with otherwise treatable tinnitus will be excluded.

Subjects who have a history of psychotic disorders or dementia will be excluded.

These psychotic symptoms will constitute exclusion from the study:
- delusions of reference
- persecutory delusions
- religious delusions
- grandiose delusions
- somatic delusions
- delusional guilt
- poverty or nihilism
- delusions of jealousy
- delusions of mind reading
- delusions of being controlled
- delusions of thought-broadcasting
- auditory hallucinations
- visual hallucinations
- tactile hallucinations
- gustatory and olfactory hallucinations

Subjects who report having a recent (within 2-year) history of alcohol or drug abuse or dependence other than tobacco or caffeine will be excluded.

Subjects who use hearing aids will be excluded from the study.
Subjects who present with sudden or fluctuating hearing loss will be excluded. Subjects with tinnitus associated with otologic disease (e.g., Meniere’s Disease) or other co-occurring diseases affecting vestibular dysfunction will be excluded.

**Contact**

Caroline J Kendall, phone +1 (203) 932-5711 ext 5459, Caroline. Kendall@va.gov
Robert D Kerns, PhD, +1 (203) 937-3841, robert.kerns@va.gov

**Location**

VA Connecticut Health Care System (West Haven), Not yet recruiting, West Haven, Connecticut, United States, 06516

**Study chairs or principal investigators**

Robert D. Kerns, PhD, VA Connecticut Health Care System (West Haven)

**Responsible Party**

Department of Veteran Affairs

**Study ID Numbers**

C6324P

**Last Updated**

April 14, 2009

**Record first received**

July 23, 2008

**ClinicalTrials.gov Identifier**

NCT00724152

**Health Authority**

United States: Federal Government

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**PET-CT to Target and Validate rTMS as Treatment for Tinnitus**

<table>
<thead>
<tr>
<th>Current status</th>
<th>ongoing, but not yet recruiting</th>
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</thead>
<tbody>
<tr>
<td>Sponsors and collaborators</td>
<td>University of Arkansas</td>
</tr>
<tr>
<td></td>
<td>Tinnitus Research Consortium</td>
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<tr>
<td>Information provided by</td>
<td>University of Arkansas</td>
</tr>
<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT00926237</td>
</tr>
<tr>
<td>Purpose</td>
<td>One out of every five people experiences tinnitus (a ringing, buzzing, or roaring sound in the ear) ranging from mild to severe impairment. To date, there are no effective therapies available that have been shown to decrease tinnitus loudness. The purpose of this study is to develop a new treatment option for tinnitus using a technique called Repetitive Transcranial Magnetic Stimulation (rTMS), which will hopefully prove to be an effective means of alleviating or reducing the symptoms of tinnitus.</td>
</tr>
<tr>
<td>Condition(s)</td>
<td>Tinnitus</td>
</tr>
<tr>
<td>Interventions</td>
<td>Device: Repetitive Transcranial Magnetic Stimulation (rTMS) - ACTIVE</td>
</tr>
<tr>
<td></td>
<td>Device: Repetitive Transcranial Magnetic Stimulation (rTMS) - SHAM</td>
</tr>
<tr>
<td>Phase</td>
<td>Phase IV</td>
</tr>
<tr>
<td>Study type and design</td>
<td>Interventional; Treatment, Randomized, Double Blind (Subject, Investigator), Placebo Control, Crossover Assignment, Safety/Efficacy Study</td>
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<td>----------------------</td>
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</tr>
<tr>
<td>Official title</td>
<td>PET-CT to Target and Validate rTMS as Treatment for Tinnitus.</td>
</tr>
<tr>
<td>Detailed description</td>
<td>This research is being conducted at the University of Arkansas for Medical Sciences (UAMS). Up to 10 subjects, including males and females ages 19-80 years old and of all races, and with tinnitus that is severe enough to seek medical attention, will be enrolled in this study. All participants will be evaluated by Dr. Dornhoffer in the Hearing and Balance Clinic at UAMS, including a modified physical examination and hearing tests, prior to beginning therapy with rTMS in order to rule out any medically treatable causes of tinnitus. An MRI scan of the head may or may not be required, depending upon the results of this evaluation, in order to rule out specific middle ear pathologies. In addition, all participants will undergo PET-CT scans of the brain before and after their first week of therapy with rTMS. The results of these PET-CT scans will be used both to target the rTMS therapy over a brain region believed to be involved in causing the tinnitus sensation and to validate the therapeutic effect of rTMS upon that region of the brain following rTMS therapy. This study will require participation in at least two weeks (5 weekdays) of rTMS sessions, including both an active week and a sham (or placebo) week. At the completion of these two weeks, subjects who have noticed an improvement in their tinnitus will have the option of participating in a maintenance rTMS program lasting up to 12 additional weeks. Subjects who have not noticed any improvement in their tinnitus will have the option of participating in one additional week of active rTMS therapy delivered to the opposite side of their brain. If this cross-over rTMS therapy results in an improvement of their tinnitus, then these subjects will also have the option of participating in the maintenance rTMS program for up to 12 additional weeks.</td>
</tr>
</tbody>
</table>
| Arms                 | 1. Active/Sham Protocol: Sham Comparator  
All subjects complete the initial two weeks of rTMS sessions, which include 5 active sessions and 5 sham sessions. Subjects are randomized so that half will begin with active while the other half will begin with sham rTMS. Active and sham weeks are separated for each subject by an interval of no less than 7 days.  
2. Cross-over (rTMS to opposite hemisphere in non-responders): Active Comparator  
Subjects who do not respond initially to active rTMS have the option of receiving 5 days of active stimulation delivered to a homologous region of the opposite cerebral hemisphere.  
3. Maintenance rTMS: Active Comparator  
Subjects who respond to either the initial week of active rTMS or the cross-over week of active rTMS have the option of participating in a maintenance rTMS program involving up to 6 additional sessions of therapy, each consisting of 3 days of active rTMS treatment. Maintenance sessions will be scheduled as the subject’s tinnitus returns to a baseline level. |
### Assigned Interventions

1. **Device: Repetitive Transcranial Magnetic Stimulation (rTMS) - ACTIVE**
   
   Active rTMS will be targeted according to the following decision tree:
   1) an accessible region of asymmetric cortical activation on PET within the temporal lobe; 2) to auditory cortex in the superior temporal gyrus opposite the ear with loudest tinnitus; 3) to the same region in the left temporal lobe. Active stimulation will be delivered at 110% of motor threshold (MT) at a frequency of 1 Hz for a duration of 30 minutes, for a total of 1800 magnetic pulses per session (and a total of 5 sessions per week of active rTMS therapy).

2. **Device: Repetitive Transcranial Magnetic Stimulation (rTMS) - SHAM**
   
   Sham rTMS will be targeted using a commercially available sham coil and delivered to an accessible region of asymmetric cortical activation within the temporal lobe in a manner identical to that for active rTMS. Scalp electrodes are used to stimulate the temporalis muscle electrically during sham stimulation to replicate the feel of active TMS.

3. **Device: Repetitive Transcranial Magnetic Stimulation (rTMS) - ACTIVE**
   
   Active rTMS will be targeted according to the following decision tree:
   1) an accessible region of asymmetric cortical activation on PET within the temporal lobe; 2) to auditory cortex in the superior temporal gyrus opposite the ear with loudest tinnitus; 3) to the same region in the left temporal lobe. Active stimulation will be delivered at 110% of motor threshold (MT) at a frequency of 1 Hz for a duration of 30 minutes, for a total of 1800 magnetic pulses per session (and a total of 5 sessions per week of active rTMS therapy).

### Primary Outcomes

- Change in tinnitus perception, as measured over time using a subjective visual analog rating scale [Time Frame: At subject enrollment, before and after each active or sham rTMS session, and via daily tinnitus log lasting for up to 6 months following rTMS therapy] [Designated as safety issue: No]

- Change in metabolic activity from pre-treatment to post-treatment PET-CT brain scans for the brain regions targeted with rTMS therapy, calculated as the difference of the asymmetry ratios for each [Time Frame: PET-CT scans obtained before and immediately following the first week of rTMS therapy (sham and active)] [Designated as safety issue: No]

### Secondary Outcomes

- Change in hearing threshold [Time Frame: Audiology evaluations obtained before and after the initial two weeks of rTMS therapy] [Designated as safety issue: Yes]
<table>
<thead>
<tr>
<th>Expected total Enrollment</th>
<th>10</th>
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<tr>
<td>Study start</td>
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<tr>
<td>Estimated study completion date</td>
<td>January 2010</td>
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<tr>
<td>Estimated primary completion date</td>
<td>January 2010 (Final data collection date for primary outcome measure)</td>
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<td>Participants (age)</td>
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<td>Gender</td>
<td>Both</td>
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<tr>
<td>Accepts health volunteers</td>
<td>No</td>
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</table>
| Eligibility Inclusion Criteria | • Diagnosis of tinnitus established through a history and physical exam performed by the study physician  
  • Subjects 19-80 years of age  
  • Tinnitus present for at least 6 months and severe enough to seek medical attention  
  • Subjects taking SSRI's (a class of anti-depressant medications) for depression related to tinnitus must be stable on their current dose for at least 3 months and must not alter their dose or medication during their involvement with this study  
  • Subjects must agree to avoid consuming alcohol within 72 hours of each rTMS session  
  • Female subjects of childbearing potential must demonstrate a negative pregnancy test during their initial clinic visit and must agree to use effective contraception during their participation in this study  
  • Subjects must sign an informed consent and agree to comply with study and follow-up procedures, including completion of all necessary questionnaires and testing (audiology evaluation, clinic visit, and two PET-CT brain scans), as well as being video-recorded for safety purposes during rTMS sessions  
  • Subjects must speak and comprehend English adequately to understand and complete any study-related instructions and questionnaires |
### Eligibility Exclusion Criteria

- Subjects or any of their 1st-degree relatives must not have been diagnosed with epilepsy
- Subjects must not have a history of seizure disorder or migraines
- Subjects must not have any history of a brain aneurysm, stroke, previous cranial neurosurgery, acoustic neuroma, glomus tumor, active Menière’s Disease, profound hearing loss (greater than 90 dB at 4000 Hz), or any major neurological or psychiatric disorders (excluding depression or anxiety related to tinnitus)
- Subjects must not have any history of a head injury that resulted in a loss of consciousness for more than 10 minutes
- Subjects must not have any metal implants or devices in the head, neck, or chest (including a pacemaker)
- Subjects must not have severe claustrophobia (may interfere with obtaining PET-CT scans)
- Subjects must not be pregnant or refuse to utilize effective contraception during their participation in this study
- Subjects must not have any history of Bipolar Disease.

### Contact

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### Locations

University of Arkansas for Medical Sciences, Little Rock, Arkansas, United States, 72205

### Study chairs or principal investigators

- John Dornhoffer, MD, UAMS Department of Otolaryngology
- Mark Mennemeier, PhD, UAMS Department of Neurosciences (study director)

### Responsible party

UAMS Department of Otolaryngology (John Dornhoffer, MD)

### Study ID Numbers

109033

### Last Updated

June 22, 2009

### Record first received

June 19, 2009

### ClinicalTrials.gov Identifier

NCT00926237

### Health Authority

United States: Institutional Review Board

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### Clinical Investigation on the Acoustic Stimulation in the Treatment of Chronic Tinnitus

<table>
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<tr>
<th>Current status</th>
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<tr>
<td>Sponsors and collaborators</td>
<td>ANM Adaptive Neuromodulation GmbH</td>
</tr>
<tr>
<td>Information provided by</td>
<td>ANM Adaptive Neuromodulation GmbH</td>
</tr>
<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT00927121</td>
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</tbody>
</table>
**Purpose**

There are many treatments for chronic tinnitus that have been claimed, with varying degrees of statistical reliability. None of those treatments can eradicate the tinnitus completely. Some therapies can reduce the tinnitus symptoms (loudness, annoyance) up to 30%. Thus there is still a need of new treatments that can reduce considerably the tinnitus symptoms and improve the QOL of subjects.

**Trial objectives:**

- The aim of this trial is the improvement of the QOL (quality of live) by reducing the Tinnitus- Symptoms of the patient.
- To confirm the efficacy and safety of the coordinated reset technology.

These objectives will be assessed:

- By subjective and objective measurements of the Tinnitus symptoms, loudness and annoyance.

**Condition(s)**

Chronic Tonal Tinnitus

**Interventions**

Device: Acoustic CR-Stimulator ANM//Technology: Acoustic coordinated reset

**Phase**

I, II

**Study type and design**

Interventional; Treatment, Randomized, Single Blind (Subject), Parallel Assignment, Safety/Efficacy Study

**Official title**

I Prospective Clinical Investigation on the Acoustic Stimulation With the “Coordinated Reset of Neural Subpopulations” in the Treatment of Chronic Tinnitus

**Arms**

- Group 1 : G_1: Active Comparator  
  G_1: stimulation for 4 - 6 hours a day, 4 tones per sequence
- Group 2 :G_2: Active Comparator  
  G_2: stimulation for 4 - 6 hours a day with 12-tone sequences
- Group3 : G_3: Active Comparator  
  G_3: stimulation for 4 - 6 hours a day, 4 tones per sequence with a signal controlled by EEG measurement
- Group 4 : G_4: Active Comparator  
  G_4: stimulation for 1 hour a day, 4 tones per sequence
- Group 5 : G_5: Placebo Comparator  
  G_5: stimulation with placebo-tone

**Assigned interventions**

G_1: Device: Acoustic CR-Stimulator ANM//Technology: Acoustic coordinated reset

The CR-stimulation was originally developed by Prof. Dr. Dr. Peter Tass for deep brain stimulation (DBS). The CR-stimulation through high frequency short pulses causes a neuronal reorganization in the stimulated brain area establishing a normal neuronal activity. Based on intensive modeling studies, experimental proof of concept (POC) animal studies and a clinical POC, we proved that the pathologic activity can be recuperated to a desynchronized/healthy state with the acoustic CR-stimulation.

The acoustic CR-stimulation signal will be generated by the ANM CR-Stimulator and transmitted to the ears through a speaker system.
The CR-stimulation was originally developed by Prof. Dr. Dr. Peter Tass for deep brain stimulation (DBS). The CR-stimulation through high frequency short pulses causes a neuronal reorganization in the stimulated brain area establishing a normal neuronal activity. Based on intensive modeling studies, experimental proof of concept (POC) animal studies and a clinical POC, we proved that the pathologic activity can be recuperated to a desynchronized/healthy state with the acoustic CR-stimulation. The acoustic CR-stimulation signal will be generated by the ANM CR-Stimulator and transmitted to the ears through a speaker system.
| Eligibility Inclusion Criteria | • right-handed subjects  
|                               | • 19-65 years of age  
|                               | • debilitating unilateral or bilateral tinnitus  
|                               | • Experiencing the presence of phantom auditory perception for >6 months  
|                               | • Tinnitus Handicap Questionnaire score of >30  

| Eligibility Exclusion Criteria | • significant neurological disease  
|                               | • acoustic neuromas or glomus tumors  
|                               | • active Meniere’s disease  
|                               | • profound hearing loss  
|                               | • non English speaking  
|                               | • personal or family history of epilepsy  
|                               | • personal history of head injury, aneurysm, stroke, previous cranial neurosurgery, neurological or psychiatric disorders, metal implants in the head or neck, a pacemaker, pregnancy, migraines,  
|                               | • medications that lower seizure threshold and are contraindicated  
|                               | • individuals who have been taking certain medications  
|                               | • claustrophobia  
|                               | • patients who do not exhibit significant cortical asymmetries on PET  

| Contact | John Dornhoffer, MD, phone +1 501-686-5016, DornhofferJohnl@uams.edu  
|         | Brenda Speed, phone +1 501-686-5140, SpeedBrendaO@uams.edu  

| Locations | United States, Arkansas, University of Arkansas for Medical Sciences, recruiting, Little Rock, Arkansas, United States, 72205  

| Study chairs or principal investigators | John Dornhoffer, MD, University of Arkansas  

| Responsible party | The University of Arkansas for Medical Sciences (Carole Hamon)  

| Study ID Numbers | 51817  

| Last Updated | January 10, 2008  

| Record first received | May 22, 2006  

| ClinicalTrials.gov Identifier | NCT00329524  

| Health Authority | United States: Institutional Review Board  

|
Open-Lable, Long-Term Treatment Study, to Assess the Long-Term Safety and Tolerability and Efficacy of Neramexane in Patients With Subjective Tinnitus (OLLTT)

<table>
<thead>
<tr>
<th>Current status</th>
<th>enrolling participants by invitation only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsors and collaborators</td>
<td>Merz Pharmaceuticals GmbH</td>
</tr>
<tr>
<td>Information provided by</td>
<td>Merz Pharmaceuticals GmbH</td>
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<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT00827008</td>
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<tr>
<td>Purpose</td>
<td>The purpose of this study is to investigate the long-term safety and tolerability and efficacy of neramxane mesylate in the long-term treatment of subjective tinnitus after a double-blind randomized placebo controlled study</td>
</tr>
<tr>
<td>Condition(s)</td>
<td>Subjective Tinnitus</td>
</tr>
<tr>
<td>Interventions</td>
<td>Drug: Neramexane mesylate</td>
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<tr>
<td>Phase</td>
<td>III</td>
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<td>Study type and design</td>
<td>Interventional; Treatment, Non-Randomized, Open Label, Uncontrolled, Single Group Assignment, Safety/Efficacy Study</td>
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<tr>
<td>Official title:</td>
<td>An Open-Lable, Long-Term Treatment Study to Assess the Long-Term Safety and Tolerability and Efficacy of Neramexane With Subjective Tinnitus</td>
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<tr>
<td>Arms:</td>
<td>1, verum: Experimental</td>
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<tr>
<td>Assigned Interventions</td>
<td>Drug: Neramexane mesylate</td>
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<tr>
<td>Up-titration treatment period of 5 weeks up to 75mg Neramexane mesylate oral per day followed by 49 weeks treatment maintenance</td>
<td>TBF-12 factorial scores, individual responder rate, Tinnitus Rating Scale, Sleep Questionnaire, safety parameters, population pharmacokinetics, optional pharmacogenetics</td>
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<td>Primary Outcome Measures:</td>
<td>Descriptive analyses of TBF-12 (Tinnitus-Beeinträchtigungs-Fragebogen 12 &quot;Tinnitus Handicap Inventory 12&quot;)total score and its subscores, of the Tinnitus Rating Scale and its single items as well as of SF-36 and safety/tolerability parameters [ Time Frame: 54 weeks ] [ Designated as safety issue: Yes ]</td>
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<td>Participants (age)</td>
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<td>Both</td>
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<td>Accepts health volunteers</td>
<td>No</td>
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| Eligibility Inclusion Criteria | • Male or female patients who have succesfully completed one of the double-blind Phase 3 studys of Merz with Neramxane mesylate  
• patients aged equal or older 18 but not older than 75 years with clinical diagnosis of first onset, persistant (i.e. tinnitus should never be absent for more than 24 hours in a row), subjective, uni-or bilateral subacute tinnitus at the timepoint of the lead-in study |
<table>
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<td>• clinical diagnosis of intermittent or pulsatile tinnitus</td>
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<td>• Patients who have tinnitus as a concomitant symptom of an otological/neurological disease (such as otitis media, Menière’s disease, otosclerosis etc.)</td>
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<table>
<thead>
<tr>
<th>Contact</th>
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<tbody>
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<table>
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<th>Locations</th>
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<tbody>
<tr>
<td>Prim. Dr. Robert Jakse, Graz, Austria, 8020</td>
</tr>
<tr>
<td>Dr. Christof Pauli (PI: Prim. Dr. Peter Ostertag), Kufstein, Austria, 6330</td>
</tr>
<tr>
<td>Dr. Susanne Grobschegg, Vienna, Austria, 1090</td>
</tr>
<tr>
<td>Dr. Robert Bodlaj, Lichtenfels, Germany, 96215</td>
</tr>
<tr>
<td>Dr. PD Suckfüll, München, Germany, 81377</td>
</tr>
<tr>
<td>Dr. Gieselmann, Werner, Heiligenhaus, Germany, 42579</td>
</tr>
<tr>
<td>Dr. Dannesberger, Lorsch, Germany, 64653</td>
</tr>
<tr>
<td>Dr. Norbert Staab, Schlüchtern, Germany, 36381</td>
</tr>
<tr>
<td>Dr. Klaus Peter Jayme, Darmstadt, Germany, 64283</td>
</tr>
<tr>
<td>Dr. Susanne Wiedemann, Nuernberg, Germany, 90443</td>
</tr>
<tr>
<td>Dr. Christian Dörr, Dresden, Germany, 01277</td>
</tr>
<tr>
<td>Dr. med. Frank Reintjes, Braunschweig, Germany, 38100</td>
</tr>
<tr>
<td>Dr. med. Ulrike Walter, Nürnberg, Germany, 90402</td>
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<tr>
<td>Dr. Wolfgang Lotte, Iserlohn, Germany, 58642</td>
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<td>Dr. Reiner Lehmman, Berlin, Germany, 13125</td>
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<tr>
<td>Dr. med. Norbert Pasch, Aachen, Germany, 52074</td>
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<td>DM Helena Sigal, Chemnitz, Germany, 09120</td>
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<tr>
<td>Dr. Hannelore Neumaier, Wiesbaden, Germany, 65183</td>
</tr>
<tr>
<td>Dr. Dr. med. Hans-Detlev Stahl, Leipzig, Germany, 04103</td>
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<td>Dr. Kühne, Elisabeth, Halle, Saale, Germany, 06112</td>
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<table>
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<th>Responsible party</th>
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<tr>
<td>Merz Pharmaceuticals GmbH (Dr. Janos Csikos, Medical Expert)</td>
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<tr>
<th>Health Authority</th>
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<td>Austria: Ethikkommission; United States: Food and Drug Administration</td>
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# Intervention for Reduced Sound Tolerance

<table>
<thead>
<tr>
<th>Current status</th>
<th>currently recruiting participants</th>
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| Sponsors and collaborators | University of Alabama, Tuscaloosa  
                             | University of Maryland  
                             | University of Memphis |
| ClinicalTrials.gov Identifier | NCT00890526 |
| Purpose                | Hyperacusis is the intolerance to sound levels that normally are judged acceptably loud to others. The presence of hyperacusis (diagnosed or undiagnosed) can be an important reason why some persons reject amplified sound from hearing aids. Tinnitus Retraining Therapy (TRT), originally proposed for the treatment of persons with debilitating tinnitus, offers the significant secondary benefit of increased Loudness Discomfort Levels (LDLs), along with expansion of the dynamic range for loudness. TRT uses both counseling and sound therapy from daily exposure to soft sound from bilateral noise generator devices (NGs) and has been promoted as an intervention for hyperacusis. The hypothesis of this investigational study is that the counseling and sound therapy principles used in TRT can be applied successfully to treat hearing-impaired hearing-aid candidates with reduced sound tolerance who are otherwise should benefit from hearing aids. |
| Condition:             | Hyperacusis |
| Intervention:          | Other: Sound Therapy (Tinnitus Retraining Therapy)  
                             | Other: Counseling (Tinnitus Retraining Therapy)  
                             | Other: No Counseling  
                             | Other: Placebo Sound Therapy |
| Phase                  | I |
| Study type and design  | Intervventional; Treatment, Randomized, Double Blind (Subject, Caregiver, Investigator), Factorial Assignment, Efficacy Study |
| Official title:        | Intervention for Reduced Sound Tolerance |
| Detailed Description   | Hyperacusis is the intolerance to sound levels that normally are judged acceptably loud to others. The presence of hyperacusis (diagnosed or undiagnosed) can be an important reason why some persons reject amplified sound from hearing aids. Tinnitus Retraining Therapy (TRT), originally proposed for the treatment of persons with debilitating tinnitus, offers the significant secondary benefit of increased Loudness Discomfort Levels (LDLs), along with expansion of the dynamic range for loudness. TRT uses both counseling and sound therapy from daily exposure to soft sound from bilateral noise generator devices (NGs) and has been promoted as an intervention for hyperacusis. The hypothesis of this investigational study is that the counseling and sound therapy principles used in TRT can be applied successfully to treat hearing-impaired hearing-aid candidates with reduced sound tolerance who are otherwise should benefit from hearing aids. |
The current study is being implemented as a randomized, double-blind, placebo-controlled trial to assess the efficacy of a TRT-based intervention for reduced sound tolerance in hearing-aid eligible persons with hyperacusis and/or restricted dynamic ranges. The trial design allows for the evaluation of the efficacy of partial treatments, including the effects of counseling separately from the effects of sound therapy. Forty hearing-impaired subjects (without primary tinnitus) are being assigned randomly to one of four treatment groups: 1) full treatment, both counseling and sound-therapy (n=10); 2) counseling with placebo sound therapy (n=10); 3) sound therapy without counseling (n=10); and 4) placebo sound therapy without counseling (n=10).

Subjects are being evaluated at least monthly, typically for five months or more, on a variety of audiometric tests, including LDLs, the Contour Test for Loudness for tones and speech, word recognition measured at each session's comfortable and loud levels, and electrophysiological measures.

| Arms | 1: Experimental  
Full treatment = Counseling + sound therapy.  
2: Experimental  
Counseling + placebo sound therapy.  
3: Experimental  
No Counseling + Sound Therapy  
4: Placebo Comparator  
No counseling + Placebo sound therapy. |
|------|----------------------------------|

| Assigned Interventions | 1: Other: Sound Therapy (Tinnitus Retraining Therapy)  
The conventional sound therapy will be achieved with commercially available noise generators. Our clinic uses General Hearing Instruments (OHI) model Tranquil devices as noise sources for TRT. These flexible devices offer an adjustable volume control, with a frequency response extending from ~500 to 8000 Hz. Matched devices will be fitted binaurally and adjusted to each individual ear to achieve audibility of the noise sources (assessed by slight threshold shifts, typically 10-15 dB, across the audiometric frequency range above 500 Hz). The sound pressure level output and frequency response of each noise source will be measured and documented using both real ear and standard electroacoustic methodologies. Each subject will be carefully instructed as to care of the instruments and correct volume setting. The bilateral noise generators will be used chronically during the intervention period except during sleep.  
Other: Counseling (Tinnitus Retraining Therapy)  
The directive counseling to be used will include an in-depth participatory discussion with the patient to review audiometric and functional test results, along with the anatomy and physiology of the auditory system. A minimum of two hours will be scheduled to impart this information to the patients so that they will have a clear understanding of the disorder based upon the most current scientific data. The counseling will be focused on educating the patient, neutralizing their negative emotional association with the hyperacusis, and discussing their treatment. |
2: Other: Counseling (Tinnitus Retraining Therapy)

The directive counseling to be used will include an in-depth participatory discussion with the patient to review audiometric and functional test results, along with the anatomy and physiology of the auditory system. A minimum of two hours will be scheduled to impart this information to the patients so that they will have a clear understanding of the disorder based upon the most current scientific data. The counseling will be focused on educating the patient, neutralizing their negative emotional association with the hyperacusis, and discussing their treatment.

Other: Placebo Sound Therapy

The placebo sound therapy will use factory-modified GHI Tranquil noise generators, which will appear identical to the conventional Tranquil devices.

The placebo Tranquil devices will have a control sensor installed to detect insertion of the device in the ear canal. When the sensor detects the insertion of the placebo device into the ear canal it will trigger gradual decay of the sound output from the placebo device. The time constant of the decaying noise output will be sufficiently long to allow the clinician time to set the volume of each binaural set of devices and to instruct the patient in their use before any noticeable sound attenuation occurs.

3: Other: Sound Therapy (Tinnitus Retraining Therapy)

The conventional sound therapy will be achieved with commercially available noise generators. Our clinic uses General Hearing Instruments (OHI) model Tranquil devices as noise sources for TRT.

These flexible devices offer an adjustable volume control, with a frequency response extending from ~500 to 8000 Hz. Matched devices will be fitted binaurally and adjusted to each individual ear to achieve audibility of the noise sources (assessed by slight threshold shifts, typically 10-15 dB, across the audiometric frequency range above 500 Hz). The sound pressure level output and frequency response of each noise source will be measured and documented using both real ear and standard electroacoustic methodologies. Each subject will be carefully instructed as to care of the instruments and correct volume setting. The bilateral noise generators will be used chronically during the intervention period except during sleep.

Other: No Counseling

Patients who are enrolled in Arms 3 and 4 of this study will not be offered directive counseling, but will be fitted with either conventional or placebo noise generators for their sound therapy components. These patients will be told only that their treatment for hyperacusis uses sound therapy.

Otherwise, in the instrument fitting appointment (either for the conventional instrument or the placebo device), these patients will receive the same instruction in the care and use of sound generators as those patients enrolled in Treatment Arms 1 and 2 of the clinical trial.
Patients who are enrolled in Arms 3 and 4 of this study will not be offered directive counseling, but will be fitted with either conventional or placebo noise generators for their sound therapy components. These patients will be told only that their treatment for hyperacusis uses sound therapy.

Otherwise, in the instrument fitting appointment (either for the conventional instrument or the placebo device), these patients will receive the same instruction in the care and use of sound generators as those patients enrolled in Treatment Arms 1 and 2 of the clinical trial.

Other: Placebo Sound Therapy

The placebo sound therapy will use factory-modified GHI Tranquil noise generators, which will appear identical to the conventional Tranquil devices.

The placebo Tranquil devices will have a control sensor installed to detect insertion of the device in the ear canal. When the sensor detects the insertion of the placebo device into the ear canal it will trigger gradual decay of the sound output from the placebo device. The time constant of the decaying noise output will be sufficiently long to allow the clinician time to set the volume of each binaural set of devices and to instruct the patient in their use before any noticeable sound attenuation occurs.

Primary Outcome Measures: 

>=dB-10 change in loudness discomfort level. [ Time Frame: 5 consecutive monthly appointments ] [ Designated as safety issue: No ]

Secondary Outcome Measures: Change in the contour 7. [ Time Frame: 5 consecutive monthly appointments ] [ Designated as safety issue: No ]

Expected total Enrollment 36

Study start July 2002

Estimated Study Completion Date: September 2009

Estimated Primary Completion Date: September 2009 (Final data collection date for primary outcome measure)

Gender Both

Accepts health volunteers No

Eligibility Inclusion Criteria

- One hundred adults, who have hearing losses and who have unsuccessfully used hearing aids because of tolerance problems (hyperacusis).
- All subjects must be committed to the use of amplification if and when the hyperacusis is resolved.
- Each patient will have demonstrable hyperacusis, but will be free from tinnitus, and must be willing to wear and use binaural in-the-ear sound generators (or placebo generators) chronically as prescribed
| Eligibility Exclusion Criteria | • Evidence of conductive, mixed hearing loss, or CNS disease.  
• Abnormal tone and/or acoustic reflex decay will also preclude subject participation because of the potential for these patients to adapt to the chronic sound therapy. |
|-------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Contact                       | Craig Formby, PhD, 205-348-1847, cformby@as.ua.edu  
Monica Hawley-Kaczka, PhD  
Univ. of Maryland - Baltimore, Baltimore, Maryland, United States, Craig Formby, PhD; recruiting |
| Responsible Party             | UATuscaloosa (Director of Research Compliance) |
| Study ID Numbers              | DC004678, 7R01DC004678-06 |
| Last Updated                  | May 18, 2009 |
| Record first received         | April 28, 2009 |
| ClinicalTrials.gov Identifier | NCT00890526 |
| Health Authority              | Institutional Review Board |

**PTC299 for Treatment of Neurofibromatosis Type 2**

<table>
<thead>
<tr>
<th>Current status</th>
<th>currently recruiting participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsors and collaborators</td>
<td>PTC Therapeutics</td>
</tr>
<tr>
<td>Information provided by</td>
<td>PTC Therapeutics</td>
</tr>
<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT00911248</td>
</tr>
<tr>
<td>Purpose</td>
<td>Formation of new blood vessels (angiogenesis) is important for tumor growth in neurofibromatosis type 2 (NF2). It is known that tumors make a protein called vascular endothelial growth factor (VEGF) and there are higher levels of VEGF in the tumors and blood of many patients with NF2. VEGF stimulates the formation of blood vessels that supply the tumor with nutrients and oxygen. PTC299 is an oral drug that has been shown to decrease production of VEGF in animal models of human cancer. In these animal models, oral PTC299 administration decreases VEGF levels in the tumor and in the bloodstream, decreases blood vessel numbers in the tumor, and significantly slows or halts tumor growth. Safety studies in research animals indicate good tolerability at doses and drug levels that are higher than those planned for the clinical studies. Results from Phase 1a studies in healthy volunteers indicate that PTC299 achieves levels of PTC299 in the bloodstream that are known to be active in animal models of human tumor. This Phase 2 study is designed to test the hypothesis that PTC299 will be tolerable and will show evidence of VEGF reduction, antitumor activity, and hearing improvement when administered orally to patients with NF2.</td>
</tr>
<tr>
<td>Condition:</td>
<td>Neurofibromatosis 2</td>
</tr>
<tr>
<td>Intervention:</td>
<td>Drug: PTC299</td>
</tr>
<tr>
<td>Phase</td>
<td>II</td>
</tr>
<tr>
<td>--------------------</td>
<td>---------------------------------------------------------------------</td>
</tr>
<tr>
<td>Study type and design</td>
<td>Interventional; Treatment, Open Label, Single Group Assignment, Safety/Efficacy Study</td>
</tr>
<tr>
<td>Official title:</td>
<td>A Phase 2 Study to Assess the Efficacy, Safety, and Pharmacodynamic Activity of PTC299 in Patients With Neurofibromatosis Type 2</td>
</tr>
<tr>
<td>Detailed Description</td>
<td>The study will be conducted in 2 stages. In Stage 1 of the study, 11 patients will receive daily treatment with PTC299 administered at 100 mg/dose twice per day for up to 1 year or until tumor progression. If no subject responds with tumor shrinkage or an improvement in hearing, then the study will be stopped. If ≥1 out of 11 subjects respond, then the study will proceed to Stage 2 to enroll an additional 14 subjects for a total of 25 subjects.</td>
</tr>
<tr>
<td>Arms</td>
<td>PTC299: Experimental PTC299 administered at 100 mg/dose twice per day</td>
</tr>
<tr>
<td>Assigned Interventions</td>
<td>Drug: PTC299 PTC299 will be administered orally at 100 mg/dose twice per day for up to 1 year or until tumor progression</td>
</tr>
<tr>
<td>Primary Outcome Measures:</td>
<td>To assess the effects of PTC299 on tumor volume and/or word recognition in patients with NF2. [ Time Frame: 48 weeks ] [ Designated as safety issue: No ]</td>
</tr>
</tbody>
</table>
| Secondary Outcome Measures: | • To assess the effects of PTC299 on pure tone thresholds, brainstem auditory evoked responses (BAERs), and otoacoustic emissions (OAEs) in patients with NF2 [ Time Frame: 48 weeks ] [ Designated as safety issue: No ]  
• To determine if PTC299 alters the perception of tinnitus [ Time Frame: 48 weeks ] [ Designated as safety issue: No ]  
• To evaluate the effects of PTC299 on tumor blood flow [ Time Frame: 48 weeks ] [ Designated as safety issue: No ]  
• To assess the effects of PTC299 on concentrations of circulating angiogenic factors or cytokines [ Time Frame: 48 weeks ] [ Designated as safety issue: No ]  
• To describe the PTC299 safety profile [ Time Frame: 48 weeks ] [ Designated as safety issue: Yes ]  
• To evaluate compliance with PTC299 treatment [ Time Frame: 48 weeks ] [ Designated as safety issue: No ]  
• To assess PTC299 plasma exposure over time [ Time Frame: 48 weeks ] [ Designated as safety issue: No ] |
<p>| Expected total Enrollment | 25                                                                 |
| Study start         | July 2009                                                           |
| Estimated Study Completion Date: | May 2011                                                            |
| Estimated Primary Completion Date: | May 2011 (Final data collection date for primary outcome measure |
| Participants (age)  | 18 Years and older                                                 |</p>
<table>
<thead>
<tr>
<th>Gender</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accepts health volunteers</td>
<td>No</td>
</tr>
<tr>
<td><strong>Eligibility Inclusion Criteria</strong></td>
<td></td>
</tr>
<tr>
<td>• Age ≥18 years</td>
<td></td>
</tr>
<tr>
<td>• Diagnosis of NF2</td>
<td></td>
</tr>
<tr>
<td>• Presence of vestibular schwannomas</td>
<td></td>
</tr>
<tr>
<td>• Evidence of progressive increase in vestibular schwannoma size or worsening hearing loss due to vestibular schwannoma</td>
<td></td>
</tr>
<tr>
<td>• Adequate functional status (Karnofsky Performance Score ≥60)</td>
<td></td>
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<tr>
<td>• Adequate bone marrow, liver, kidney function</td>
<td></td>
</tr>
<tr>
<td>• If sexually active, willingness to use effective barrier or medical contraception</td>
<td></td>
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<tr>
<td>• For women of childbearing potential, no pregnancy or breast-feeding</td>
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</tr>
<tr>
<td>• Discontinuation of other therapies (except corticosteroids) for the treatment of NF2 and resolution of any acute toxic effects of prior therapies</td>
<td></td>
</tr>
<tr>
<td>• Willingness and ability to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions</td>
<td></td>
</tr>
<tr>
<td>• Willingness to provide informed consent</td>
<td></td>
</tr>
<tr>
<td><strong>Eligibility Exclusion Criteria</strong></td>
<td></td>
</tr>
<tr>
<td>• Uncontrolled hypertension, major bleeding, HIV infection, or recent acute cardiovascular event</td>
<td></td>
</tr>
<tr>
<td>• Prior exposure to another anti-angiogenic therapy (eg, bevacizumab, sunitinib)</td>
<td></td>
</tr>
<tr>
<td><strong>Contact</strong></td>
<td>Diane M Goetz, (908) 912-9256; <a href="mailto:dgoetz@ptcbio.com">dgoetz@ptcbio.com</a></td>
</tr>
<tr>
<td><strong>Locations</strong></td>
<td>United States, Massachusetts, Massachusetts General Hospital, Boston, Massachusetts, United States, 02114, Scott Plotkin, MD, 617-724-8770</td>
</tr>
<tr>
<td><strong>Principal Investigator</strong></td>
<td>Langdon Miller, MD, PTC Therapeutics</td>
</tr>
<tr>
<td><strong>Responsible Party</strong></td>
<td>PTC Therapeutics, Inc. (Harry Miao, MD, PhD)</td>
</tr>
<tr>
<td><strong>Study ID Numbers</strong></td>
<td>PTC299-ONC-007-NF2, NF080100</td>
</tr>
<tr>
<td><strong>Last Updated</strong></td>
<td>July 10, 2009</td>
</tr>
<tr>
<td><strong>Record first received</strong></td>
<td>May 28, 2009</td>
</tr>
<tr>
<td><strong>ClinicalTrials.gov Identifier</strong></td>
<td>NCT00911248</td>
</tr>
<tr>
<td><strong>Health Authority</strong></td>
<td>Food and Drug Administration</td>
</tr>
</tbody>
</table>
**A clinical study of bojungikgitang and banhabaekchulchonmatang in adult tinnitus patients**

<table>
<thead>
<tr>
<th><strong>Current status</strong></th>
<th>ongoing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sponsors and collaborators</strong></td>
<td>Korea Health Industry Development Institute (KHIDI) (South Korea)</td>
</tr>
<tr>
<td><strong>Information provided by</strong></td>
<td>Korea Health Industry Development Institute (KHIDI) (South Korea) - The 2008 Traditional Korean Medicine Research and Development Project</td>
</tr>
<tr>
<td><strong>ISRCTN</strong></td>
<td>ISRCTN23691284</td>
</tr>
<tr>
<td><strong>Hypothesis</strong></td>
<td>This study is aimed to evaluate the efficacy and safety of bojungikgitang and banhabaekchulchonmatang in adult tinnitus patients.</td>
</tr>
<tr>
<td><strong>Condition:</strong></td>
<td>Tinnitus</td>
</tr>
</tbody>
</table>
| **Intervention:** | This study is a randomised, double-blind, placebo-controlled study. Participants will receive bojungikgitang, banhabaekchulchonmatang, or a placebo-drug for 8 weeks. Oral administration occurs according to the following statements:
1. Patients in group 1 receive bojungikgitang and instructions on how to make a tea; they take a packet of the medicine (12.52 g) with tepid water for three times a day after meal
2. Patients in group 2 receive banhabaekchulchonmatang and instructions on how to make a tea; they take a packet of the medicine (12.52 g) with tepid water for three times a day after meal
3. Patients in group 3 receive the placebo medicine (powdered extract), used in the same way as with group 1 and 2
The total duration of all arms is 11 weeks. Timepoints are as follows:
Visit 1: screening
Visit 2: treatment initiation, participants will receive bojungikgitang, banhabaekchulchonmatang, or a placebo-drug for 8 weeks
Visit 3: 4 weeks later of first medication, follow-up
Visit 4: 8 weeks later of first medication, follow-up and treatment finish
Visit 5: 10 weeks later of first medication, follow-up |
<p>| <strong>Study type and design</strong> | Randomised phase III double-blind three-arm placebo-controlled trial |
| <strong>Official title:</strong> | A clinical study of bojungikgitang and banhabaekchulchonmatang in adult tinnitus patients: a randomised, double-blind, three-arm, placebo-controlled trial |</p>
<table>
<thead>
<tr>
<th><strong>Primary Outcome Measures:</strong></th>
<th><strong>Efficacy:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tinnitus Handicap Inventory (THI): the purpose of this questionnaire is to identify difficulties that may be experienced because of tinnitus:</td>
<td></td>
</tr>
<tr>
<td>1.1. F: Functional subscale (11 factors)</td>
<td></td>
</tr>
<tr>
<td>1.2. E: Emotional subscale (9 factors)</td>
<td></td>
</tr>
<tr>
<td>1.3. C: Catastrophic subscale (5 factors)</td>
<td></td>
</tr>
<tr>
<td>Measured at baseline (1 week before treatment initiation), 4 weeks later of the first medication, 8 weeks later of the first medication, follow up (2 weeks later of treatment period)</td>
<td></td>
</tr>
</tbody>
</table>

**Safety:**

1. Complete blood cell count, erythrocyte sedimentation rate (ESR)  
2. Blood chemistry  
3. Urine analysis  
4. Chest antero-posterior (PA) film  
5. Brain computed tomography (CT)  
6. Otologic examination  
7. Vital signs; measured at baseline, treatment initiation, 4 weeks later of the first medication, 8 weeks later of the first medication

### Secondary Outcome Measures:

<table>
<thead>
<tr>
<th><strong>Efficacy:</strong></th>
</tr>
</thead>
</table>
| 1. Acoustic Examination (AE)  
2. Visual Analogue Scale (VAS)  
3. EQ-5D  
4. Health Utilities Index Mark 3 (HUI3) Measured at baseline, 8 weeks later of the first medication, follow up |

| **Expected total Enrollment** | 120 |
| **Study start** | 01/03/2009 |
| **Estimated Study Completion Date:** | 30/09/2009 |

**Eligibility Inclusion Criteria**

1. Age greater than 19 years, either sex  
2. Typical conditions of intermittent or continuous tinnitus  
2.1. The duration of more than 3 months  
2.2. Involuntary perception of the concept of a sound without the presence of an external source  
3. Agreed not to receive another treatment during the clinical trial period  
4. Written and informed consent
| Eligibility Exclusion Criteria | 1. Receiving other forms of tinnitus treatments  
2. Underlying disease or history:  
2.1. Otitis media  
2.2. Acoustic tumour  
2.3. Intracranial lesion  
2.4. Inner ear malformation  
2.5. Head trauma  
2.6. Ototoxic drug medication, etc.  
3. Women in pregnancy and lactation or without contraception  
4. Other clinical trial within the last 1 month  
5. Auditory surgery, a major surgery or a blood transfusion within the last 1 month  
6. Hypersensitiveness or allergy of drugs  
7. Disease which can affect the absorption of drugs or disordered digestion after surgery related to the disease  
8. History of neuropsychitric abnormality:  
8.1. Manic-depression  
8.2. Schizophrenia  
8.3. Alcoholism  
8.4. Drug addiction, etc.  
9. Cannot understand a written consent or follow this study:  
9.1. Mental retardation  
9.2. Mental or emotional problems  
10. Judged by expert that they are inappropriate to participate in this study |
| Contact | Dr Donghyo Lee, Wonkwang University Oriental Medical Center, 1126-1 Sanbon-dong, Gunpo, Korea, South, 435-040; secretop17@naver.com |
| Sponsors Details | Korea Health Industry Development Institute (KHIDI) (South Korea), 57-1 Noryangjin-dong, Dongjak-gu, Seoul, Korea, South, 158-800, phone: +82 (0)2 2194 7227, Fax: +82 (0)2 824 1762; withingrace@khidi.or.kr |
| Responsible Party | -- |
| Study ID Numbers | B08-0045-AM0829-08N1-00010A |
| ISRCTN | ISRCTN23691284 |
| Health Authority | Wonkwang University Oriental Medical Center Ethics Committee gave approval on the 25th February 2009 |