Dear friends and colleagues,

Tomorrow the 5th TRI Meeting starts and many of you are already on the way to Buffalo in the United States. Two hundred clinicians and scientists from all over the world will meet to discuss the latest findings in tinnitus research, to exchange ideas and to identify the most promising directions for further research. Many more were interested in coming, but registration had to be closed several weeks ago, because of limited space capacities.

When TRI started 5 years ago, with the belief that the neuroscientific approach would be the key for finding a solution for tinnitus, this approach had not been the mainstream in tinnitus research. Over time, more and more clinicians have shared our belief and - even more important - more and more bright neuroscientists have discovered tinnitus as their major research area. Thus, in the last years this approach has made incredible progress, which all participants will witness this weekend in Buffalo.

„The Neuroscience of Tinnitus“ is becoming an established research area. But does it also hold the promise to bring us a cure for tinnitus? Still there is no breakthrough. However, animal research and functional and structural neuroimaging have generated a more detailed understanding of the pathophysiological mechanisms of the different forms of tinnitus by identifying new potential therapeutic targets and new treatment approaches. To give an example: It was the pivotal work of neuroscientists like Arnaud Norena, Jos Eggermont, Nathan Weisz, Thomas Elbert or Rudolfo Llinas who identified hypersynchrony in the auditory cortex as a prerequisite for the perception of tinnitus. Thus reducing this increased neuronal synchrony was identified as a therapeutic target, which finally prompted a computational neuroscientist like Peter Tass to apply the principle of „coordinated reset“ as an innovative treatment. With very promising pilot data, this is a new therapeutic approach, which would not have been possible without the neuroscientific background. We all know that there is a long way going from a new idea and promising pilot data to a new treatment applicable in clinical routine. Moreover, we have to accept that this requires more time, more time than we and our patients would like. Thus, even if we try our best to accelerate the gap from „proof of concept“ to „routine therapy“, patience is still mandated. However, we are convinced that with the current knowledge there are new treatments on the horizon, helping many patients to overcome their daily torture.

Thus, with scientific enthusiasm during the next days in Buffalo and keeping in mind the suffering of so many tinnitus patients we will meet remembering that a „Cure of Tinnitus“ is the single most important goal of our work.

Belén Elgoyhen  Dirk De Ridder  Berthold Langguth  Sylvia Dorner-Mitschke

Here you find the ABSTRACTS of the 5th TRI Conference.
RESEARCH HIGHLIGHTS

Gouveris H, Schuler-Schmidt W, Mewes T, Mann W. Intratympanic Dexamethasone/Hyaluronic Acid Mix as an Adjunct to Intravenous Steroid and Vasoactive Treatment in Patients With Severe Idiopathic Sudden Sensorineural Hearing Loss. Otol Neurotol. 2011 Jun 3;


These three studies demonstrate the efficacy of intratympanic steroid therapy as add-on resp. salvage therapy in addition to systemic steroids in the treatment of sudden hearing loss.


This animal study highlights the relevance of temporal dynamics in the development of tinnitus. Whereas in the early phase increased activity in the central auditory pathways depends on auditory input, this is not any more the case at a later stage.


By demonstrating an increased risk of tinnitus among mp3 users, this study highlights the relevance of prevention.


This study proposes an in-vitro model to screen pharmaceutical compounds for the treatment of tinnitus. If this model turns out to be a valid predictor for clinical effects, it will open new dimensions in the search for a tinnitus drug.


In this review the relevance of alpha oscillations for the pathophysiology of tinnitus is discussed in a larger context.


This animal study highlights the involvement of the ventral cochlear nucleus in the pathophysiology of tinnitus.


In this magnetencephalographic study the authors were able to differentiate the neuronal correlates of bottom-up and top-down processing in the auditory system.


Here the levels of evidence of generally recommended strategies of tinnitus management were reviewed.
**NEWS**

**International State-of-the-Science Meeting on Blast-Related Tinnitus**

**3rd in the International State-of-the-Science Meeting Series**

**November 15-16, 2011**

The Department of Defense (DoD) Blast Injury Research Program Coordinating Office (PCO) established a “State of the Science Meeting Series” to assist in identifying knowledge gaps pertaining to key blast injury issues. These narrowly focused meetings help us determine what is known and what is unknown about a particular blast injury topic. These meetings are designed to bring in top researchers, worldwide, from academia, DoD, other government organizations, and industry to share their expertise in helping us focus future research investments that address these gaps.

The DoD Blast Injury Research PCO, along with the Office of Naval Research and the DoD Hearing Center of Excellence, will co-host an International State-of-the-Science meeting on “Blast-Related Tinnitus” on November 15-16, 2011 in Northern Virginia.

Acoustic trauma is the most frequently observed injury in our warfighters returning from Afghanistan and Iraq. Not surprisingly, hearing loss and tinnitus are the respective #1 and #2 compensatory illnesses reported by the U.S. Department of Veterans Affairs. In 2005, Congress mandated that the Institute of Medicine (IOM) carry out a study assessing several issues related to noise induced hearing loss and tinnitus associated with service in the Armed Forces since World War II. The IOM study recommended the Services improve the prevention of, and surveillance for, hearing loss and tinnitus. The DoD Hearing Center of Excellence identified tinnitus as a top research initiative in their organizational concept of operation plan due to the enormous effect tinnitus has on the warfighter and veteran populations.

The objectives of this State-of-the-Science Meeting are to:

- Identify the cause of tinnitus and determine its association, if any, with Post Traumatic Stress Disorder (PTSD) and Traumatic Brain Injury (TBI)
- Determine if there are existing diagnostic tools that can be used to objectively identify tinnitus
- Identify and prioritize the research gaps that exist in standardizing methods used in the treatment of tinnitus

On Day 1 of the meeting, experts from scientific, medical, and academic communities will present their work; and on Day 2, all attendees will participate in working groups. Your participation will help achieve the objectives and address the following questions:

- What are the current theories concerning the neurobiological basis of tinnitus?
- Is there substantial evidence that tinnitus is associated with PTSD and TBI. If so, what are the common biomarkers?
- What are the current technological approaches to tinnitus diagnosis?
- How can research standardize methods of effective tinnitus treatment?

Approximately 130 subject matter experts from the DoD, other Federal agencies, academia, industry and the international community will be invited to participate in this meeting.

- If you are interested in presenting in the area of Diagnostics, Etiology, Treatment, or Tinnitus related to TBI/PTSD, please indicate your intention and focus area in the form at [https://blastinjuryresearch.amedd.army.mil/index.cfm?f=application.pco_sos_2011_tinnitus](https://blastinjuryresearch.amedd.army.mil/index.cfm?f=application.pco_sos_2011_tinnitus) AND submit a 200-500 word abstract of your presentation to Lt Col Robert Shull at robert.shull@amedd.army.mil NLT midnight on August 29, 2011

There is no registration fee for this meeting.
Sixth International TRI Tinnitus Conference

Tinnitus:
The Art and Science of Innovation

June 13th - 16th, 2012
Bruges, Belgium

Organized by:
Brai²n, University Hospital Antwerp, Belgium,
and the
Tinnitus Research Initiative

Information about this meeting is available on
http://www.brai2n.net/tri2012

Organizing Committee:
Dirk De Ridder, M.D. Ph.D.
Paul Van de Heyning, M.D., Ph.D.
Berthold Langguth, M.D., Ph.D.
Ana Belén Elgoyhen, Ph.D.
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Upcoming Meetings

Meetings exclusively dedicated to Tinnitus are marked red

August 2011

Biology of the inner ear - experimental and analytical approaches

When: August 7 – 27, 2011
Where: Woods Hole, MA, USA
Detailed Information: http://courses.mbl.edu/bie

5th International TRI Tinnitus Conference. The Neuroscience of Tinnitus

When: August 19 – 21, 2011
Where: Buffalo, NY, USA
E-Mail: meetings@tinnitusresearch.org
Detailed Information: http://www.tinnitusresearch.org/

September 2011

Nineteenth annual conference on the management of the tinnitus patient

When: September 8 – 10, 2011
Where: Iowa, USA
Contact: conferences@uiowa.edu

American Academy of Otolaryngology, Head and Neck Surgery Annual Meeting

When: September 11 – 14, 2011
Where: San Francisco, CA, USA
Detailed Information: http://www.entnet.org

28. Politzer Society Meeting

When: September 29 – October 1, 2011
Where: Zappeion Exhibition Hall, Athens, Greece
Contact: GOLDAIR Congress, 15 Panepistimiou Avenue, 10564 Athens, Greece
Phone: +30 210 3274570
Fax: +30 210 3311021
E-Mail: info@politzer-athens2011.gr
and/or congress@goldair.gr
8th Meeting of the British Society of Neuro-Otology

When: October 14, 2011
Where: National Hospital for Neurology and Neurosurgery, Queen Square, London
Contact: Miss J. Mills, Neuro-Otology Group, Imperial College London, Charing Cross Hospital
        Fulham Palace Road London W6 8RF
Phone: +44 (0)208 846 7285
Fax: +44 (0)208 846 7577
E-Mail: neuro-otology@imperial.ac.uk
Detailed Information: http://www.bsno.org.uk/8th%20meeting.html

56th International Congress of Hearing Aid Acousticians

When: October 19 – 21, 2011
Where: CongressCenter Nürnberg, CCN East, Germany
Detailed Information: http://www.euha.org

Asia Pacific Symposium on Cochlear Implant and Related Science

When: October 26 – 28, 2011
Where: Korea
Detailed Information: http://knuh.knu.ac.kr

162nd Meeting of the Acoustical Society of America

When: October 31 – November 4, 2011
Where: San Diego, California, United States
E-Mail: asa@aip.org
Detailed Information: http://asa.aip.org/meetings.html

International State-of-the-Science Meeting on Blast-Related Tinnitus

When: November 15 – November 16, 2011
Where: Northern Virginia, United States
E-Mail: robert.shull@amedd.army.mil
I Epidemiology


Tinnitus Clinic, Institute of Physiology and Pathology of Hearing, AK Kampinos 1, 01-943 Warsaw, Poland.

Introduction. Although tinnitus often has a significant impact on individual’s life, there are still few reports relating to tinnitus in children. In our tinnitus clinic, children with distressing tinnitus constitute about 0.5% of all our patients. Objectives. The aim of this study was to analyse children with troublesome tinnitus as regards epidemiology, audiological profile, and preliminary effects of the therapy. Methods. A retrospective study was carried out involving the cases of 143 children consulted in our Tinnitus Clinic in 2009. The selected group with troublesome tinnitus was evaluated and classified for proper category of Tinnitus Retraining Therapy (TRT). Results. The study showed that 41.3% of the children suffered from bothersome tinnitus. In this group 44.1% of the patients demonstrated normal hearing. The success of the therapy after 6 months was estimated on 81.4% of significant improvement. Conclusions. It is recommended that a questionnaire include an inquiry about the presence of tinnitus during hearing screening tests.

The influence of military service on auditory health and the efficacy of a hearing conservation program.

Muhr P, Rosenhall U.

Department of Clinical Neurosciences, Clinical Science, Intervention and Technology, Division of ENT and Hearing, Karolinska Institute; The Swedish Armed Forces, The Occupational Health Centre at the Garrison of Halmstad, Sweden.

The influence of military service on self-assessed hearing symptoms and measured auditory function was studied as well as the efficacy of the Hearing Conservation Program (HCP) of the Swedish Armed Forces. 839 conscripts were recruited for the study at reporting to military service. They were all exposed to noise over the risk-limits from weapons and vehicles and used earmuffs and/or earplugs. Questionnaires and pure tone screening audiometry were studied at the start and the end of the military service. Retrospective information regarding audiometry at conscription before military service was included as control. The prevalence values of tinnitus were 23% before and 32% after the service and of sensitivity to noise 16% and 19% respectively. The prevalence values of hearing impairment were 6.3% at conscription, 14.5% at reporting to military service, and 24% after the training period. The incidence values of hearing decline were 3.7% during the period with no military noise exposure and 6.6% during the military service. Acoustic accident increased the risk of worsened tinnitus and sensitivity to noise four times and for high frequency hearing decline six times. We observed elevated prevalence values of tinnitus, sensitivity to noise and hearing impairment at discharge compared to before military service. We observed an elevated risk of hearing decline during military service. Acoustic accident increased the risk of tinnitus, noise sensitivity and hearing decline. We suggest improvements regarding inclusion criteria for military service, and for education regarding the HCP.
Incidence of tinnitus in mp3 player users.
[Article in English, Portuguese]

Figueiredo RR, Azevedo AA, Oliveira PM, Amorim SP, Rios AG, Baptista V.

area of concentration - ENT, Rio de Janeiro Federal University.

Exposure to loud noise is one of the main causes of tinnitus. AIM: To analyze the incidence of tinnitus in mp3 player users and non-users. MATERIAL AND METHOD: One hundred subjects aged from 15 to 30 years were enrolled, 54 of them were regular mp3 player users and 46 were not. Patients with continuous tinnitus for at least 6 months completed the Tinnitus Handicap Inventory (THI) and were tested with high frequency audiometry and transient-evoked otoacoustic emissions (TAOE). STUDY DESIGN: A cross-sectional cohort study. RESULTS: The incidence of tinnitus in non-users was about 8%; in mp3 player users it was about 28%, a statistically significant difference. Hearing thresholds at 8kHz were significantly higher in tinnitus patients that used mp3 portable players. TAOE were reduced at 2 kHz in the users group. No statistically significant difference was found in the THI scores between the two groups. CONCLUSION: Tinnitus was more frequent in teenagers and young adults who regularly listen to mp3 music in players. Moreover, the incidence of tinnitus among mp3 player users was associated with higher hearing thresholds at 8 kHz and lower TOAE at 2 kHz.

Prevalence of Tinnitus in Community-Dwelling Japanese Adults.
J Epidemiol. 2011 Jun 4


Department of Epidemiology & Preventive Medicine, Gifu University Graduate School of Medicine.

Background: Several studies have reported the prevalence of tinnitus among general populations; however, most of these studies were conducted in Europe or the United States. We estimated the prevalence of tinnitus among the general adult population in Japan. Methods: The subjects were participants in the Takayama Study, a population-based cohort study. In 2002, a total of 14 423 adults (6450 men and 7973 women) aged 45 to 79 years responded to a self-administered questionnaire that inquired about history of tinnitus, which was defined as episodes lasting longer than 5 minutes, excluding those occurring immediately after noise exposure. Respondents were also asked about the loudness and severity of tinnitus. Results: Overall, 11.9% of the subjects reported having tinnitus; the percentage was somewhat higher among men (13.2%) than women (10.8%). The prevalence of tinnitus increased with age in both sexes. Approximately 0.4% of the overall population reported that tinnitus had a severe effect on their ability to lead a normal life. Medical history of hypertension or ischemic heart diseases, use of steroid or antihypertensive medication, and employment as a factory worker or machine operator were associated with tinnitus status in both men and women. Conclusions: Tinnitus is relatively common in Japan. Although the use of various definitions of tinnitus in different studies makes it difficult to compare prevalence among populations, the present prevalence estimate was similar to those in studies in Europe and the United States.


Money A, Carder M, Turner S, Hussey L, Agius R

Centre for Occupational and Environmental Health, Health Sciences Group, School of Community Based Medicine, University of Manchester, Oxford Road, Manchester M13 9PL, UK.

BACKGROUND: Noise-induced hearing loss (NIHL) from prolonged occupational exposure to noise continues to rank among the top worldwide work-related ill-health problems. AIMS: To provide an overview of incident cases based on work-related audiological ill-health data collected over a 9-year period from occupational physicians (OPs), audiological physicians (APs),
general practitioners and otorhinolaryngologists.  

METHODS: Analysis of numerator data reported by physicians to surveillance schemes within The Health and Occupation Reporting network (THOR). The actual cases were multiplied by the sampling ratio to provide estimated numerator numbers, followed by calculation of incidence rates using denominator data derived from the Labour Force Survey and from surveys of participating OPs.  

RESULTS: Two thousand five hundred and eighty-two estimated cases (2584 estimated diagnoses) were received from OPs (Occupational Physicians Reporting Activity [OPRA]), and 2192 estimated cases (3208 estimated diagnoses) of work-related audiological ill-health were received from consultant APs [Occupational Surveillance Scheme for Audiological physicians (OSSA)] from 1998 to 2006. Cases where the causal agent was noise exposure (NIHL and tinnitus) made up of 95 and 97% of all cases reported to OPRA and OSSA, respectively. The annual average incidence rate for noise-induced audiological disorders was 7.9 [95% confidence interval (CI) 4.6-11.1] per 100 000 persons employed (OPRA) and 0.8 (95% CI 0.7-1.0) per 100 000 persons employed (OSSA). Workers with the highest incidence were older males employed in public administration and defence and the manufacture of metals.  

CONCLUSIONS: THOR data show that diagnoses related to work-related noise exposure (NIHL/tinnitus), as reported to THOR, remain important health problems, despite preventive measures being in place.  

Tinnitus in the General Population With a Focus on Noise and Stress: A Public Health Study.  
Baigi A, Oden A, Almlid-Larsen V, Barrenäs ML, Holgers KM.  
1Department of Research and Development, Halland County Council, Halmstad, Sweden; 2Department of Primary Health Care, The Sahlgrenska Academy at Gothenburg University, Gothenburg, Sweden; 3Department of Mathematical Sciences, Chalmers University of Technology, Gothenburg, Sweden; 4Department of Habilitation and Health, Region Västra Götaland, Hearing Clinic, Borås, Sweden; 5Göteborg Pediatric Growth Research Center, Department of Pediatrics, Institute of Clinical Sciences, The Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden; and 6Department of Health Sciences at Jönköping Academy, University of Jönköping, Jönköping, Sweden.  

OBJECTIVES: To evaluate the influence of noise and stress on the probability of tinnitus in the general population. DESIGN: Questionnaire data from 12,166 subjects. RESULTS: Each year of age increased the odds ratio of tinnitus by about 3%. Men generally showed a higher risk for tinnitus compared with women. Exposure to noise and stress emerged important for the probability of tinnitus. However, for the transition from mild to severe tinnitus, stress turned out to be especially important. CONCLUSIONS: Stress management strategies should be included in hearing conservation programs, especially for individuals with mild tinnitus who report a high stress load.  

[The prevalence of tinnitus in 7-year-old children in the eastern of Poland].  
[Article in Polish]  
Instytut Fizjologii i Patologii Słuchu, Klinika Szumów Usznyc, Warszawa. d.koziak@ifps.org.pl  

INTRODUCTION: Tinnitus in children is still rarely mentioned in medical literature. The prevalence of pediatric tinnitus has been reported to range between 3-37% and higher in children with hearing loss. OBJECTIVES: The objective of this study was to estimate the prevalence of the tinnitus in 7 years old children and to conduct statistical analysis of the relation between tinnitus and hearing loss. MATERIAL AND METHODS: In this study 60 212 children and their parents were asked about the presence of tinnitus by answering a questionnaire at home. Additionally, children were asked if they can hear noise in their ears or head, before hand hearing screening test at school was conducted. The hearing screening test was performed using screening audiometer with air conduction.
RESULTS: The results showed that tinnitus was present in group of 8164 children (13.6%). Between children directly asked for tinnitus, 33% mentioned of having it. Over 75% of children did not complained of tinnitus spontaneously to parents. Children with hearing loss reported tinnitus twice more comparing to children with normal hearing. CONCLUSIONS: Tinnitus is frequent complain among 7 years old children. Children with hearing loss reported tinnitus twice more comparing to children with normal hearing. It is recommended to include to a questionnaire an inquiry about the presence of tinnitus during hearing screening tests performed recently more frequently at primary schools for early detection and diagnosis of tinnitus.

II Pathophysiology

Pharmacological drugs inducing ototoxicity, vestibular symptoms and tinnitus: a reasoned and updated guide.


Cianfrone G, Pentangelo D, Cianfrone E, Mazzei F, Turchetta R, Orlando MP, Altissimi G.

Department of Otolaryngology, Audiology and Phoniatrics, Umberto I University Hospital, Sapienza University, Rome, Italy. giancarlo.cianfrone@uniroma1.it

The present work on drug-induced ototoxicity, tinnitus and vertigo represents the update and revision of a previous guide to adverse drug reactions for italian physicians (2005). The panorama of drug-induced side effects causing ototoxicity or symptoms such as tinnitus or dizziness and vertigo has enlarged in recent years, thanks to a better knowledge and a more specific attention of pharmaceutical firms and drug-control institutions. In daily clinical practice, there is a need for the family physician and the ENT specialist or audiologist (also in consideration of the possible medico-legal implications) to focus the attention on the possible risk of otological side effects. This would allow a clinical risk-benefit evaluation, weighing the possible clinical advantage in their field of competence against possible otological side-effects. The list of active ingredients and drugs is subdivided in categories based on their audiological and otoneurological side-effects, that have been signaled by the drug companies and/or ministerial notes. Drugs have also been subcategorized with regards to the field in which they are applied, the therapeutic indications and the clinical behaviour. They have also been organized in alphabetical order, for an easier consultation. The guide above, even if initially conceived for being used in Italy, also presents a more general and international interest, expecially as for as the concepts of pharmacology and the features of the active ingredients are concerned. The guide is, therefore, useful as for as we are concerned to any physician, regardless of the country he/she operates in.

Chemical neuroprotection in the cochlea: The modulation of dopamine release from lateral olivocochlear efferents.


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The prevalence of sensorineural hearing loss is increasing worldwide, mainly due to ageing, increased noise exposure and cardiovascular risk factors. Several papers dealt with the mechanisms underlying the primary causes of impaired hearing and eventual deafness, including the damage and loss of auditory hair cells; however, very little is known about the protective mechanisms that exist for hearing. Several recent investigations have implicated dopamine (DA) in a neuroprotective circuit for the cochlea. The lateral olivocochlear (LOC) efferents provide axonal innervation of the inner hair cell afferent synapses and release DA and other substances in response to different stimuli. Under ischemic conditions or during noise exposure, DA has been proven to play a neuroprotective role against glutamate excitotoxicity. This review summarises what is currently known about the modulation of DA
release in the cochlea, using primarily in vitro experimental data. Based on recent knowledge, there could be two functional subgroups within the LOC fibres, i.e., the DA- and GABA-containing projections. In this review, we attempt to show the neurochemical interactions between these two subsystems. Other aspects of cochlear neurotransmission are also discussed to provide a complete picture of cochlear dopaminergic function in physiological and pathophysiological cases with particular reference to excitotoxicity. Copyright © 2011 Elsevier B.V. All rights reserved.

**Relationship between noise-induced hearing-loss, persistent tinnitus and growth-associated protein 43 expression in the rat cochlear nucleus: does synaptic plasticity in ventral cochlear nucleus suppress tinnitus?**

Neuroscience. 2011 Jul 28. [Epub ahead of print]

Kraus SK, Ding D, Jiang H, Lobarinas E, Sun W, Salvi RJ.

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Aberrant, lesion-induced neuroplastic changes in the auditory pathway are believed to give rise to the phantom sound of tinnitus. Noise-induced cochlear damage can induce extensive fiber growth and synaptogenesis in the cochlear nucleus, but it is currently unclear if these changes are linked to tinnitus. To address this issue, we unilaterally exposed nine rats to narrow-band noise centered at 12 kHz at 126 dB sound pressure level (SPL) for 2 h and sacrificed them 10 weeks later for evaluation of synaptic plasticity (growth-associated protein 43 [GAP-43] expression) in the cochlear nucleus. Noise-exposed rats along with three age-matched controls were screened for tinnitus-like behavior with gap prepulse inhibition of the acoustic startle (GPIAS) before, 1-10 days after, and 8-10 weeks after the noise exposure. All nine noise-exposed rats showed similar patterns of severe hair cell loss at high- and mid-frequency regions in the exposed ear. Eight of the nine showed strong up-regulation of GAP-43 in auditory nerve fibers and pronounced shrinkage of the ventral cochlear nucleus (VCN) on the noise-exposed side, and strong up-regulation of GAP-43 in the medial ventral VCN, but not in the lateral VCN or the dorsal cochlear nucleus. GAP-43 up-regulation in VCN was significantly greater in Noise-No-Tinnitus rats than in Noise-Tinnitus rats. One Noise-No-Tinnitus rat showed no up-regulation of GAP-43 in auditory nerve fibers and only little VCN shrinkage, suggesting that auditory nerve degeneration plays a role in tinnitus generation. Our results suggest that noise-induced tinnitus is suppressed by strong up-regulation of GAP-43 in the medial VCN. GAP-43 up-regulation most likely originates from medial olivocochlear neurons. Their increased excitatory input on inhibitory neurons in VCN may possibly reduce central hyperactivity and tinnitus. Copyright © 2011. Published by Elsevier Ltd.

**Relationship between auditory thresholds, central spontaneous activity, and hair cell loss after acoustic trauma.**

J Comp Neurol. 2011 Sep 1;519(13):2637-47. doi: 10.1002/cne.22644

Mulders WH, Ding D, Salvi R, Robertson D.

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Acoustic trauma caused by exposure to a very loud sound increases spontaneous activity in central auditory structures such as the inferior colliculus. This hyperactivity has been suggested as a neural substrate for tinnitus, a phantom hearing sensation. In previous studies we have described a tentative link between the frequency region of hearing impairment and the corresponding tonotopic regions in the inferior colliculus showing hyperactivity. In this study we further investigated the relationship between cochlear compound action potential threshold loss, cochlear outer and inner hair cell loss, and central hyperactivity in inferior colliculus of guinea pigs. Two weeks after a 10-kHz pure tone acoustic trauma, a tight relationship was demonstrated between the frequency region of compound action potential threshold loss and frequency regions in the inferior colliculus showing hyperactivity. Extending the
duration of the acoustic trauma from 1 to 2 hours did not result in significant increases in final cochlear threshold loss, but did result in a further increase of spontaneous firing rates in the inferior colliculus. Interestingly, hair cell loss was not present in the frequency regions where elevated cochlear thresholds and central hyperactivity were measured, suggesting that subtle changes in hair cell or primary afferent neural function are sufficient for central hyperactivity to be triggered and maintained. J. Comp. Neurol. 519:2637-2647, 2011. © 2011 Wiley-Liss, Inc.

Development of Tinnitus in CBA/CaJ Mice Following Sound Exposure.

Longenecker RJ, Galazyuk AV.

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Tinnitus, the perception of a sound without an external acoustic source, is a complex perceptual phenomenon affecting the quality of life in 17% of the adult population. Despite its ubiquity and morbidity, the pathophysiology of tinnitus is a work in progress, and there is no generally accepted cure or treatment. Development of a reliable common animal model is crucial for tinnitus research and may advance this field. The goal of this study was to develop a tinnitus mouse model. Tinnitus was induced in an experimental group of mice by an exposure to a loud (116 dB sound pressure level (SPL)) narrow band noise (one octave, centered at 16 kHz) during 1 h under anesthesia. The tinnitus was then assessed behaviorally by measuring gap induced suppression of the acoustic startle reflex. We found that a vast majority of the sound-exposed mice (86%) developed behavioral signs of tinnitus. This was a complex, long lasting, and dynamic process. On the day following exposure, all mice demonstrated signs of acute tinnitus over the entire range of sound frequencies used for testing (10-31 kHz). However, 2-3 months later, a behavioral evidence of tinnitus was evident only at a narrow frequency range (20-31 kHz) representing a presumed chronic condition. Extracellular recordings confirmed a significantly higher rate of spontaneous activity in inferior colliculus neurons in sound-exposed compared to control mice. Surprisingly, unilateral sound exposure suppresses startle responses in mice and they remained suppressed even 3 months post-exposure, whereas auditory brainstem response thresholds were completely recovered during 2 months following exposure. In summary, behavioral evidence of tinnitus can be reliably developed in mice by sound exposure, and tinnitus induction can be assessed by quantifying prepulse inhibition of the acoustic startle reflex.

Tinnitus: Models and mechanisms.

Kaltenbach JA.

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Over the past decade, there has been a burgeoning of scientific interest in the neurobiological origins of tinnitus. During this period, numerous behavioral and physiological animal models have been developed which have yielded major clues concerning the likely neural correlates of acute and chronic forms of tinnitus and the processes leading to their induction. The data increasingly converge on the view that tinnitus is a systemic problem stemming from imbalances in the excitatory and inhibitory inputs to auditory neurons. Such changes occur at multiple levels of the auditory system and involve a combination of interacting phenomena that are triggered by loss of normal input from the inner ear. This loss sets in motion a number of plastic readjustments in the central auditory system and sometimes beyond the auditory system that culminate in the induction of aberrant states of activation that include hyperactivity, bursting discharges and increases in neural synchrony. This article will review was has been learned about the biological origins of these alterations, summarize where they occur and examine the cellular and molecular mechanisms that are most likely to underlie them. Ototrauma induces sodium channel plasticity in auditory afferent neurons.

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Exposure to intense sound can cause damage to the delicate sensory and neuronal components of the cochlea leading to hearing loss. Such damage often causes the dendrites of the spiral ganglion neurons (SGN), the neurons that provide the afferent innervation of the hair cells, to swell and degenerate thus damaging the synapse. In models of neuropathic pain, axotomy, another form of afferent nerve damage, is accompanied by altered voltage-gated sodium channel (VGSC) expression, leading to neuronal hyperactivity. In this study, adult Wistar rats were exposed to noise which produced a mild, 20dB hearing threshold elevation and their VGSC expression was investigated. Quantitative PCR showed decreased Na(V)1.1 and Na(V)1.6 mRNA expression in the SGN following noise exposure (29% and 56% decrease respectively) while Na(V)1.7 mRNA expression increased by approximately 20% when compared to control rats. Immunohistochemistry extended these findings, revealing increased staining for Na(V)1.1 along the SGN dendrites and Na(V)1.7 in the cell bodies after noise. These results provide the first evidence for selective changes in VGSC expression following moderate noise-induced hearing loss and could contribute to elevated hearing thresholds and to the generation of perceptual anomalies commonly associated with cochlear damage, such as tinnitus and hyperacusis.


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Salicylate-induced ototoxicity leading to sensorineural hearing loss (SNHL) and tinnitus is well documented. However, the exact mechanisms are poorly defined. Caspase-3 is a member of the class of effector caspases and has been activated in nearly every model of apoptosis. To examine its role in salicylate-induced injury, we subjected guinea pigs to treatment with a specific inhibitor zDEVD-FMK via the round window niche (RWN) followed by a systemic injection of salicylate at a dose of 200 mg • kg(-1) • d(-1) i.p. for 10 consecutive days. For those animals administered with salicylate, immunohistochemical studies revealed that caspase-3 was activated in the spiral ganglion neurons (SGNs) and method of terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end-labeling (TUNEL) to identify neuronal apoptosis showed that fragmented nuclei were distributed in Rosenthal's canal. Topical administration of the zDEVD-FMK at a concentration of 500 mM blocked caspase-3 activation and had an effect in reducing the number of TUNEL-positive auditory neurons. In contrast, the inhibitor at a concentration of 125 or 250 mM caused no variation in the expression of activated caspase-3, or in the ratio of TUNEL-positive neurons. These results indicate that caspase-3 is a crucial mediator of apoptosis induced by salicylate in the primary auditory neuron in vivo, and suggest that the specific inhibitor at a relatively high concentration may be therapeutically beneficial in salicylate-induced apoptosis.
Plasticity of somatosensory inputs to the cochlear nucleus - Implications for tinnitus.
Hear Res. 2011 May 18. [Epub ahead of print]

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This chapter reviews evidence for functional connections of the somatosensory and auditory systems at the very lowest levels of the nervous system. Neural inputs from the dorsal root and trigeminal ganglia, as well as their brain stem nuclei, cuneate, gracilis and trigeminal, terminate in the cochlear nuclei. Terminations are primarily in the shell regions surrounding the cochlear nuclei but some terminals are found in the magnocellular regions of cochlear nucleus. The effects of stimulating these inputs on multisensory integration are shown as short and long-term, both suppressive and enhancing. Evidence that these projections are glutamatergic and are altered after cochlear damage is provided in the light of probable influences on the modulation and generation of tinnitus. Copyright © 2011 Elsevier B.V. All rights reserved.

Tinnitus is Associated With Increase in the Intima-Media Thickness of Carotid Arteries.

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INTRODUCTION: Increased intima-media thickness of carotid arteries is considered as an early indicator of atherosclerosis. The authors here aimed to assess whether tinnitus is associated with such thickening by a cross-sectional approach. METHODS: A total of 820 male (53.5 ± 9.6 years) and 528 female (54.5 ± 9.7 years) Japanese undergoing a brain screening program including ultrasonographical evaluation of carotid arteries between April 2007 and April 2009 were included in the study. Increased intima-media thickness was defined as ≥ 1 mm. Multiple logistic regression analyses were performed with adjustment for sex, age, body mass index, hypertension and smoking. RESULTS: Increased intima-media thickness was observed in 53.1% overall (in 57.6% of men and in 46.2% of women), with significant associations with tinnitus (odds ratio, 1.62; 95% confidence interval, 1.19-2.22), age, male gender and hypertension. The tinnitus link persisted after adjustment for the confounding factors. CONCLUSIONS: Tinnitus is associated with increased intima-media thickness of carotid arteries in Japanese undergoing a brain screening program.

Comparison of auditory electrophysiological responses in normal-hearing patients with and without tinnitus.

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Introduction:Tinnitus is a disturbing symptom and is often the main reason for otology referral. It is usually associated with hearing loss of varying aetiology, and is thought to begin in the cochlea, with later abnormal central activity. We hypothesise that tinnitus without hearing loss may be caused by central and subcortical abnormalities and altered outer hair cell function. Aim: To compare the auditory brainstem responses, middle latency responses and otoacoustic emissions in normal-hearing individuals with and without tinnitus. Methodology: The audiological test results of 25 normal hearing subjects with
tinnitus (age 18-45 years) were determined, and compared with those of a control group. Results: A statistically significant difference was found between study group tinnitus ears vs control group ears, as regards wave I latency prolongation, shortening of wave V and absolute I-III and I-V interpeak latency, enlargement of wave Na and Pa amplitude, and distortion product and transient evoked otoacoustic emission signal-to-noise ratios. There was no statistically significant difference between unilateral vs bilateral tinnitus ears. Conclusion: The pathogenesis and optimum management of tinnitus are still unclear. It often occurs with primary ear disease, usually associated with hearing loss, but may occur in patients with normal hearing. Observed changes in auditory brainstem and middle latency responses indicate central auditory alterations. Tinnitus involves both peripheral and central activity, and complete audiological and neurophysiological investigation is required. Management should be based on both audiological and neurophysiological findings.

A connection between the Efferent Auditory System and Noise-Induced Tinnitus Generation. Reduced contralateral suppression of TEOAEs in patients with noise-induced tinnitus.


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Background: Subjective tinnitus is an auditory perception that is not caused by external stimulation, its source being anywhere in the auditory system. Furthermore, evidence exists that exposure to noise alters cochlear micromechanics, either directly or through complex feed-back mechanisms, involving the medial olivocochlear efferent system. The aim of this study was to assess the role of the efferent auditory system in noise-induced tinnitus generation.<br />

Material/Methods: Contralateral sound-activated suppression of TEOAEs was performed in a group of 28 subjects with noise-induced tinnitus (NIT) versus a group of 35 subjects with normal hearing and tinnitus, without any history of exposure to intense occupational or recreational noise (idiopathic tinnitus-IT). Thirty healthy, normally hearing volunteers were used as controls for the efferent suppression test. Results: Suppression of the TEOAE amplitude less than 1 dB SPL was considered abnormal, giving a false positive rate of 6.7%. Eighteen out of 28 (64.3%) patients of the NIT group and 9 out of 35 (25.7%) patients of the IT group showed abnormal suppression values, which were significantly different from the controls' (p<0.0001 and p<0.045, respectively). Conclusions: The abnormal activity of the efferent auditory system in NIT cases might indicate that either the activity of the efferent fibers innervating the outer hair cells (OHCs) is impaired or that the damaged OHCs themselves respond abnormally to the efferent stimulation.

Progressive centralization of midbrain hyperactivity after acoustic trauma.
Neuroscience. 2011 Jun 24. [Epub ahead of print]

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Partial hearing loss is known to cause increased spontaneous activity at several stages of the central auditory pathways, and this phenomenon has been suggested as a possible neural substrate for tinnitus, a phantom hearing sensation. One recent study in guinea pig has suggested that approximately 6 weeks after acoustic trauma, the increased spontaneous activity in inferior colliculus is not intrinsically generated in the central nucleus but is dependent on afferent input from the cochlea. This was unexpected in view of the fact that tinnitus in human patients can persist after severing of the auditory nerve. In this study, we show that when recovery time after acoustic trauma is extended to 8 and 12 weeks, cochlear ablation does not significantly decrease the increased spontaneous activity measured in the inferior colliculus. This result demonstrates for the first time that central hyperactivity that develops...
after acoustic trauma transitions from an early stage when it is dependent on continued peripheral afferent input to a later stage in which the hyperactivity is intrinsically generated within the central nervous system. Copyright © 2011. Published by Elsevier Ltd.

**Medio-lateral postural instability in subjects with tinnitus.**


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Background: Many patients show modulation of tinnitus by gaze, jaw or neck movements, reflecting abnormal sensorimotor integration, and interaction between various inputs. Postural control is based on multi-sensory integration (visual, vestibular, somatosensory, and oculomotor) and indeed there is now evidence that posture can also be influenced by sound. Perhaps tinnitus influences posture similarly to external sound. This study examines the quality of postural performance in quiet stance in patients with modulated tinnitus. Methods: Twenty-three patients with highly modulated tinnitus were selected in the ENT service. Twelve reported exclusively or predominately left tinnitus, eight right, and three bilateral. Eighteen control subjects were also tested. Subjects were asked to fixate a target at 40 cm for 51 s; posturography was performed with the platform (Technoconcept, 40 Hz) for both the eyes open and eyes closed conditions. Results: For both conditions, tinnitus subjects showed abnormally high lateral body sway (SDx). This was corroborated by fast Fourier Transformation (FFTx) and wavelet analysis. For patients with left tinnitus only, medio-lateral sway increased significantly when looking away from the center. Conclusion: Similarly to external sound stimulation, tinnitus could influence lateral sway by activating attention shift, and perhaps vestibular responses. Poor integration of sensorimotor signals is another possibility. Such abnormalities would be accentuated in left tinnitus because of the importance of the right cerebral cortex in processing both auditory-tinnitus eye position and attention.

**Decrease of prestin expression by increased potassium concentration in organotypic cultures of the organ of Corti of newborn rats.**


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Prestin is the motor protein of the outer hair cells of the organ of Corti and a key factor in ensuring a high sensitivity level of mammalian hearing. In the present study, we examined the effects of increased extracellular potassium (K+M) concentration on the expression of prestin mRNA and the transcription factors Gata-3 and Carf in the organotypic culture of the organ of Corti of newborn rats. Mannitol and NaCl were used to analyze possible effects of hyperosmotic stress or ion-specific changes, respectively. An increase in prestin expression by a factor of 1.5-2.0 was seen in cultures grown in the presence of 5mM K+. Potassium concentration of 35 and 55mM induced a parallel decrease in prestin and Carf expression, but Gata-3 expression increased. Mannitol had no effect on gene expression whereas increased NaCl concentrations decreased prestin, but not Carf expression. The data suggest that chronic depolarization might decrease the prestin expression and possibly contribute to hearing loss and tinnitus. Copyright © 2011 Elsevier Ireland Ltd. All rights reserved.
The effects of acoustic trauma that can cause tinnitus on spatial performance in rats.
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Previous studies have shown that acoustic trauma can disrupt the firing of place cells in the hippocampus and also inhibit hippocampal neurogenesis, suggesting that such trauma might impair spatial memory. In this study, we investigated performance in the alternating T maze and Morris water maze of rats exposed to acoustic trauma (16 kHz, 110 dB SPL pure tone for 1 h), who had elevated auditory brainstem response thresholds and the psychophysical attributes of tinnitus (using a conditioned lick suppression task). To our surprise, we found that rats with tinnitus did not perform significantly differently from sham control animals in either the alternating T maze task or any aspect of the reference or working memory versions of the Morris water maze task except for a faster acquisition in T maze alternation. These results suggest that acoustic trauma and tinnitus may not impair spatial memory in rats. Copyright © 2011 IBRO. Published by Elsevier Ltd. All rights reserved.

Hyperactivity in the ventral cochlear nucleus after cochlear trauma.
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The emergence of hyperactivity in the form of elevated spontaneous firing rates after cochlear trauma has been well documented in a number of central auditory structures, including the auditory cortex, inferior colliculus, and dorsal subdivision of the cochlear nucleus. This hyperactivity is of interest as a possible neural substrate of tinnitus. Whether the ventral subdivision of the cochlear nucleus shows hyperactivity has never been investigated despite the fact that, like the dorsal division, it also receives direct input from the damaged cochlea and supplies major ascending inputs to brainstem and midbrain auditory centers. We investigated spontaneous neuronal firing rates in the ventral cochlear nucleus in a guinea pig model of cochlear trauma in which we have shown that hyperactivity consistently develops in the inferior colliculus (Mulders and Robertson, 2009). The mean spontaneous firing rates of ventral cochlear nucleus neurons was significantly elevated compared to sham controls. This hyperactivity was more evident in primary-like and onset categories of neurons. Hyperactivity in the ventral subdivision of cochlear nucleus therefore needs to be considered in relation to neural models of the genesis of tinnitus.

Cochlear changes in presbycusis with tinnitus.
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OBJECTIVES: The pathophysiology of tinnitus is obscure and its treatment is therefore elusive. Significant progress in this field can only be achieved by determining the mechanisms of tinnitus generation, and thus, histopathologic findings of the cochlea in presbycusis with tinnitus become crucial. We revealed the histopathologic findings of the cochlea in subjects with presbycusis and tinnitus. MATERIAL AND METHODS: The subjects were divided into 2 groups, presbycusis with tinnitus (tinnitus) group and presbycusis without tinnitus (control) group, with each group comprising 8 temporal bones from 8 subjects. We quantitatively analyzed the number of spiral ganglion cells, loss of cochlear inner and outer hair cells, and areas of the stria vascularis and spiral ligament.
RESULTS: There was a significantly greater loss of outer hair cells in the tinnitus group compared with the control group in the basal and upper middle turns. The stria vascularis was more atrophic in the tinnitus group compared with the control group in the basal turn.

CONCLUSIONS: Tinnitus is more common in patients with presbycusis who have more severe degeneration of outer hair cells and stria vascularis. Copyright © 2011 Elsevier Inc. All rights reserved.

A neural network model of normal and abnormal auditory information processing.  
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The ability of the brain to attenuate the response to irrelevant sensory stimulation is referred to as sensory gating. A gating deficiency has been reported in schizophrenia. To study the neural mechanisms underlying sensory gating, a neuroanatomically inspired model of auditory information processing has been developed. The mathematical model consists of lumped parameter modules representing the thalamus (TH), the thalamic reticular nucleus (TRN), auditory cortex (AC), and prefrontal cortex (PC). It was found that the membrane potential of the pyramidal cells in the PC module replicated auditory evoked potentials, recorded from the scalp of healthy individuals, in response to pure tones. Also, the model produced substantial attenuation of the response to the second of a pair of identical stimuli, just as seen in actual human experiments. We also tested the viewpoint that schizophrenia is associated with a deficit in prefrontal dopamine (DA) activity, which would lower the excitatory and inhibitory feedback gains in the AC and PC modules. Lowering these gains by less than 10% resulted in model behavior resembling the brain activity seen in schizophrenia patients, and replicated the reported gating deficits. The model suggests that the TRN plays a critical role in sensory gating, with the smaller response to a second tone arising from a reduction in inhibition of TH by the TRN. Copyright © 2011 Elsevier Ltd. All rights reserved.

Sound Processing Hierarchy within Human Auditory Cortex.  
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Both attention and masking sounds can alter auditory neural processes and affect auditory signal perception. In the present study, we investigated the complex effects of auditory-focused attention and the signal-to-noise ratio of sound stimuli on three different auditory evoked field components (auditory steady-state response, N1m, and sustained field) by means of magnetoencephalography. The results indicate that the auditory steady-state response originating in primary auditory cortex reflects the signal-to-noise ratio of physical sound inputs (bottom-up process) rather than the listener’s attentional state (top-down process), whereas the sustained field, originating in nonprimary auditory cortex, reflects the attentional state rather than the signal-to-noise ratio. The N1m was substantially influenced by both bottom-up and top-down neural processes. The differential sensitivity of the components to bottom-up and top-down neural processes, contingent on their level in the processing pathway, suggests a stream from bottom-up driven sensory neural processing to top-down driven auditory perception within human auditory cortex.
Prior Expectation Mediates Neural Adaptation to Repeated Sounds in the Auditory Cortex: An MEG Study.

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Repetition suppression, the phenomenon that the second presentation of a stimulus attenuates neural activity, is typically viewed as an automatic consequence of repeated stimulus presentation. However, a recent neuroimaging study has suggested that repetition suppression may be driven by top-down expectations. Here we examined whether and when repetition suppression can be modulated by top-down expectation. Participants listened to auditory stimuli in blocks where tone repetitions were either expected or unexpected, while we recorded ongoing neural activity using magnetoencephalography. We found robust repetition suppression in the auditory cortex for repeated tones. Interestingly, this reduction was significantly larger for expected than unexpected repetitions, both in terms of evoked activity and gamma-band synchrony. These findings indicate a role of top-down expectation in generating repetition suppression and are in line with predictive coding models of perception, in which the difference between expected and actual input is propagated from lower to higher cortical areas.

Contrast gain control in auditory cortex.

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The auditory system must represent sounds with a wide range of statistical properties. One important property is the spectrotemporal contrast in the acoustic environment: the variation in sound pressure in each frequency band, relative to the mean pressure. We show that neurons in ferret auditory cortex rescale their gain to partially compensate for the spectrotemporal contrast of recent stimulation. When contrast is low, neurons increase their gain, becoming more sensitive to small changes in the stimulus, although the effectiveness of contrast gain control is reduced at low mean levels. Gain is primarily determined by contrast near each neuron’s preferred frequency, but there is also a contribution from contrast in more distant frequency bands. Neural responses are modulated by contrast over timescales of about 100 ms. By using contrast gain control to expand or compress the representation of its inputs, the auditory system may be seeking an efficient coding of natural sounds. Copyright © 2011 Elsevier Inc. All rights reserved.

III Diagnostics

Assessment of tinnitus-related impairments and disabilities using the German THI-12: Sensitivity and stability of the scale over time.

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Abstract Objective: To evaluate the reliability, dimensionality, predictive validity, construct validity, and sensitivity to change of the THI-12 total and sub-scales as diagnostic aids to describe and quantify tinnitus-evoked reactions and evaluate treatment efficacy. Design: Explorative analysis of the German tinnitus handicap inventory (THI-12) to assess potential sensitivity to tinnitus therapy in placebo-
controlled randomized studies. Correlation analysis, including Cronbach’s coefficient and explorative common factor analysis (EFA), was conducted within and between assessments to demonstrate the construct validity, dimensionality, and factorial structure of the THI-12. Study sample: N = 618 patients suffering from subjective tinnitus who were to be screened to participate in a randomized, placebo-controlled, 16-week, longitudinal study. Results: The THI-12 can reliably diagnose tinnitus-related impairments and disabilities and assess changes over time. The test-retest coefficient for neighboured visits was $r > 0.69$, the internal consistency of the THI-12 total score was $\alpha = 0.79$ and $\alpha = 0.89$ at subsequent visits. Predictability of THI-12 total score and overall variance increased with successive measurements. The three-factorial structure allowed for evaluation of factors that affect aspects of patients’ health-related quality of life. Conclusions: The THI-12, with its three-factorial structure, is a simple, reliable, and valid instrument for the diagnosis and assessment of tinnitus and associated impairment over time.

Tinnitus in elderly patients and prognosis of mild-to-moderate congestive heart failure: a cross-sectional study with a long-term extension of the clinical follow-up.


Borghi C, Cosentino ER, Rinaldi ER, Brandolini C, Rimondi MC, Veronesi M, Cicero AF, Dormi A, Pirodda A.

BACKGROUND: The complex mechanism responsible for tinnitus, a symptom highly prevalent in elderly patients, could involve an impaired control of the microcirculation of the inner ear, particularly in patients with poor blood pressure control and impaired left ventricular (LV) function. METHODS: In order to define the relationship between the presence of tinnitus and the severity and clinical prognosis of mild-to-moderate chronic heart failure (CHF) in a large population of elderly patients (N = 958), a cross-sectional study was conducted with a long-term extension of the clinical follow-up. Blood pressure, echocardiographic parameters, brain natriuretic peptide (BNP), hospitalization, and mortality for CHF were measured. Multivariate logistic regression analysis was used to assess the association between the presence of tinnitus and some of the prognostic determinants of heart failure. RESULTS: The presence of tinnitus was ascertained in 233 patients (24.3%; mean age 74.9 +/- 6 years) and was associated with reduced systolic and diastolic blood pressure (123.1 +/- 16/67.8 +/- 9 vs 125.9 +/- 15/69.7 +/- 9; P = .027/P = .006), reduced LV ejection fraction (LVEF%; 43.6 +/- 15 vs 47.9 +/- 14%, P = .001), and increased BNP plasma levels (413.1 +/- 480 vs 286.2 +/- 357, P = .013) in comparison to patients without symptoms. The distribution of CHF functional class was shifted toward a greater severity of the disease in patients with tinnitus. Combined one-year mortality and hospitalization for CHF (events/year) was 1.43 +/- 0.2 in patients with tinnitus and 0.83 +/- 0.1 in patients without tinnitus, with an adjusted hazard ratio (HR) of 0.61 (95% confidence interval (CI): 0.37 to 0.93, P <.002). CONCLUSIONS: Our preliminary data indirectly support the hypothesis that tinnitus is associated with a worse CHF control in elderly patients and can have some important clinical implications for the early identification of patients who deserve a more aggressive management of CHF.

A Hebrew adaptation of the tinnitus handicap inventory.


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Abstract Objective: To establish a Hebrew version of the English THI. Design: The English THI (THI-E) was translated into Hebrew by two bilingual investigators, independently. A third investigator then constructed the final Hebrew THI version (THI-H) from the two translations. This version was administered to fifty consecutive patients at the tinnitus clinic. Participants also assessed tinnitus severity and loudness, and completed the Hebrew versions of the Beck’s depression inventory and the state anxiety inventory. Study sample: The participants were fifty consecutive patients (older than 18 years
of age, with a tinnitus lasting over three months) who were referred to a tinnitus clinic (none of them declared compensation seeking). Results: A very good internal consistency was found (α = 0.93), with significant correlation between the subscales of the THI-H and the Beck depression inventory score and the state anxiety inventory score. Conclusions: A valid and reliable THI-H questionnaire was constructed.

Variability in the Management of Idiopathic Sudden Sensorineural Hearing Loss.

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Objectives. To evaluate current trends in the management of idiopathic sudden sensorineural hearing loss (ISSNHL), determine if variance in diagnostic and treatment protocols exists, and compare diagnostic and treatment strategies of ISSNHL between nonotologists/neurotologists (NONs) and otologists/neurotologists (ONs). Study Design. Cross-sectional survey of practicing otolaryngologists. Setting. Otolaryngology practices within the United States. Subjects and Methods. In January 2010, a survey was mailed to 500 NONs and 500 ONs. Data were collected and analyzed using χ(2), standard deviations, and variance. Results. A variety and distribution of responses were seen in the definition of ISSNHL, including dB loss necessary for diagnosis, number of consecutive frequencies involved, and maximum duration of hearing loss. Differences in diagnostic tools were also seen, with 50.4% of respondents (NON 34.2%, ON 66.7%; P = .0001) always using magnetic resonance imaging in their workup. Of the total respondents, 26.7% (NON 35.0%, ON 18.3%; P < .0001) preferred oral steroids alone; 22.1% (NON 11.7%, ON 32.5%; P < .0001) preferred a combination of oral and intratympanic steroids. Of the respondents, 68.6% (NON 57.5%, ON 80.0%; P = .0003) would continue with additional treatment after partial response; 20.8% (NON 33.3%, ON 8.3%; P < .005) would retreat with oral steroids alone and 46.6% (NON 35.8%, ON 57.3%; P < .05) with intratympanic injections. Overall, 69.2% (NON 45.8%, ON 92.5%; P = .0001) were very comfortable managing ISSNHL. Conclusion. Significant differences exist in the diagnosis and treatment of ISSNHL. Such lack of uniformity highlights the need for strong evidence-based research-ultimately leading to formalized practice guidelines and educational outreach.

Endolymphatic hydrops in Meniere's disease detected by MRI after intratympanic administration of gadolinium: comparison with sudden deafness.

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The detection rate of endolymphatic hydrops was significantly higher in patients with Meniere's disease compared with those with sudden deafness, indicating that 3 T magnetic resonance imaging (MRI) with intratympanic gadolinium injection was effective in diagnosing endolymphatic hydrops.
Assessment of Health State in Patients With Tinnitus: A Comparison of the EQ-5D and HUI Mark III.

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OBJECTIVES: Expressing the outcomes of treatment in quality-adjusted life years is increasingly important as a tool to aid decision makers concerning the allocation of scarce resources within the health care sector. A quality-adjusted life year is a measure of life expectancy that is weighted by health-related quality of life. These weights are referred to as utility scores and are usually measured by multiattribute utility measures. Several studies found that different utility measures provide different estimates of the same person's level of utility. The aim of this study was to investigate which of two widely used utility measures, the EQ-5D and the HUI mark III, is preferred in a tinnitus population.

METHODS: Baseline and follow-up data on EQ-5D and HUI mark III of 429 patients of a randomized controlled clinical trial, investigating cost-effectiveness of usual care versus specialized care of tinnitus, were included. Agreement, discriminative power, and responsiveness of the health state description and the utility scores were examined.

RESULTS: Corresponding dimensions of the EQ-5D and HUI mark III showed large correlations; although ceiling effects were more frequently observed in the EQ-5D. Mean utility scores for EQ-5D (0.77; SD 0.22) and HUI mark III (0.64; SD 0.28) were significantly different (Wilcoxon signed ranks test, p < 0.001), and agreement was low to moderate (intraclass correlation coefficient = 0.53). Both health state description and utility scores of both measures discriminated between different severity groups. These groups were based on baseline scores of the Tinnitus Questionnaire. The HUI mark III had a higher ability than the EQ-5D to detect improved patients from randomly selected pairs of improved and unimproved patients.

CONCLUSION: This study shows that different utility measures lead to different health state descriptions and utility scores among tinnitus patients. However, both measures are capable of discriminating between clinically different groups. The HUI mark III is more responsive than the EQ-5D, and therefore preferred in a tinnitus population.

[The quality of diagnostic classification using abridged versions of the tinnitus questionnaire: Comparative analysis.]
[Article in German]

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BACKGROUND: There are different abridged versions of the tinnitus questionnaire (TQ) and reference values for grading tinnitus-related distress, the diagnostic value of which is unclear, as is the relation of sensitivity to specificity, as well as positive and negative predictive values. The present study is aimed at clarifying these issues and at benchmarking the existing abridged TQ versions.

PATIENTS AND METHODS: TQ data from 209 outpatients who had tinnitus for a period of at least 4 months were collected at the beginning of treatment. The rate of correct severity ratings, the quality of making a distinction between (extremely) severe and compensated/moderate tinnitus (area-under curve under the receiver-operating-characteristics curve, and rate of correct classifications), as well as positive and negative predictive values were calculated.

RESULTS: Applying unspecific reference values (independent of inpatient/outpatient status), the most
favourable evaluation was achieved by the shortest TQ version (10 items). With the 12-item version (mini-TQ), better classification was achieved when reference values specific for outpatients were applied instead of unspecific values.

**Semicircular canal dehiscence in HR multislice computed tomography: distribution, frequency, and clinical relevance.**
Eur Arch Otorhinolaryngol. 2011 Jul 8. [Epub ahead of print]

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The literature about bony defects in the semicircular canal system is highly inconsistent. Therefore, we analyzed a series of 700 high-resolution multislice CT examinations of the temporal bone for semicircular canal dehiscencies. An unselected group of ENT patients with different clinical symptoms and variable age was chosen. We found semicircular canal dehiscence in 9.6% of temporal bones, superior semicircular canal was affected mostly (8%), less common posterior semicircular canal (1.2%); only in 3 cases (0.4%), lateral semicircular canal showed dehiscence. In 60% of SSC dehiscence, we registered bilateral manifestation. The so-called „third mobile window” in semicircular canal dehiscence causes a great variety of clinical symptoms like vertigo, nystagmus, oscillopsies, hearing loss, tinnitus and autophonia. Comparison with anatomic studies shows that CT examination implies the risk of considerable overestimation; this fact emphasizes the important role of clinical and neurophysiological testing.

**IV Imaging**

**Bifrontal transcranial direct current stimulation modulates tinnitus intensity and tinnitus-distress-related brain activity.**

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Bifrontal transcranial direct current stimulation (tDCS), with the anodal electrode overlying the right and the cathodal electrode overlying the left dorsolateral prefrontal cortex, has been shown to suppress tinnitus significantly in 30% of patients. The source localized resting-state electrical activity is recorded before and after bifrontal tDCS in patients who respond to tDCS to unravel the mechanism by which tDCS suppresses tinnitus. The present electroencephalography study (N=12) provides support for the ability of bifrontal tDCS to suppress tinnitus intensity and tinnitus-related distress by modulation of the pregenual anterior cingulate cortex, parahippocampal area and right primary auditory cortex in resting-state spontaneous brain activity. These findings provide direct support for tDCS having an impact not only directly on the underlying dorsolateral prefrontal cortex but also indirectly on functionally connected brain areas relevant for tinnitus distress and tinnitus intensity, respectively. © 2011 The Authors. European Journal of Neuroscience © 2011 Federation of European Neuroscience Societies and Blackwell Publishing Ltd.
The Use of Alcohol as a Moderator for Tinnitus-Related Distress.

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Tinnitus is an auditory phantom percept with a tone, hissing, or buzzing sound in the absence of any objective physical sound source. Persons with tinnitus engage in a number of health behaviors to manage tinnitus. This can go from prescription medication, masking devices, behavioral training techniques to cortical implants. Potentially less adaptive methods of coping with tinnitus, such as the use of alcohol, are poorly studied. The purpose of this study was to further explore the neurobiological mechanism of tinnitus improvement by the use of alcohol. We observed differences in the alpha, beta and gamma frequency band when comparing resting-state EEG before and after alcohol intake. More precisely increased synchronized alpha1 activity was found in the posterior cingulate cortex and decreased synchronized alpha2 activity was demonstrated in orbitofrontal cortex, ventrolateral prefrontal cortex and subcallosal anterior cingulate cortex after alcohol intake. Increased synchronized activity was found in a region between the pregenual and dorsal anterior cingulate cortex and the left insula for beta and decreased activity in the precuneus after alcohol intake. For the gamma frequency band decreased synchronized activity in the precuneus and the posterior cingulate cortex was demonstrated after alcohol intake. Region of interest analyses in auditory cortices and parahippocampal area revealed however no differences in the different frequency bands before and after alcohol consumption.

Alpha rhythms in audition: cognitive and clinical perspectives.

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Like the visual and the sensorimotor systems, the auditory system exhibits pronounced alpha-like resting oscillatory activity. Due to the relatively small spatial extent of auditory cortical areas, this rhythmic activity is less obvious and frequently masked by non-auditory alpha-generators when recording non-invasively using magnetoencephalography (MEG) or electroencephalography (EEG). Following stimulation with sounds, marked desynchronizations can be observed between 6 and 12 Hz, which can be localized to the auditory cortex. However knowledge about the functional relevance of the auditory alpha rhythm has remained scarce so far. Results from the visual and sensorimotor system have fuelled the hypothesis of alpha activity reflecting a state of functional inhibition. The current article pursues several intentions: (1) Firstly we review and present own evidence (MEG, EEG, sEEG) for the existence of an auditory alpha-like rhythm independent of visual or motor generators, something that is occasionally met with skepticism. (2) In a second part we will discuss tinnitus and how this audiological symptom may relate to reduced background alpha. The clinical part will give an introduction into a method which aims to modulate neurophysiological activity hypothesized to underlie this distressing disorder. Using neurofeedback, one is able to directly target relevant oscillatory activity. Preliminary data point to a high potential of this approach for treating tinnitus. (3) Finally, in a cognitive neuroscientific part we will show that auditory alpha is modulated by anticipation/expectations with and without auditory stimulation. We will also introduce ideas and initial evidence that alpha oscillations are involved in the most complex capability of the auditory system, namely speech perception. The evidence presented in this article corroborates findings from other modalities, indicating that alpha-like activity functionally has an universal inhibitory role across sensory modalities.
Pharmacotherapy

A Randomized, Controlled Study Comparing the Effects of Vestipitant or Vestipitant and Paroxetine Combination in Subjects With Tinnitus.


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OBJECTIVE: Tinnitus is a common symptom that demonstrates a significant comorbidity with anxiety and depression. The novel neurokinin-1 receptor antagonist, vestipitant, has anxiolytic properties and a good safety profile. Vestipitant was investigated for potential effect against chronic tinnitus as a stand-alone treatment and in conjunction with a selective serotonin reuptake inhibitor, paroxetine. STUDY DESIGN: Randomized, double-blind, crossover study. SETTING: Tertiary neurotologic and audiologic center with additional referrals from a secondary university hospital center. PATIENTS: Twenty-four adult patients with tinnitus were randomized into the study. MAIN OUTCOME MEASURES: Visual analogue scale (VAS) measurements of tinnitus loudness (intensity), pitch and distress, VAS measurements of arousal/anxiety, Tinnitus Handicap Inventory, Quick Inventory of Depressive Symptomatology, and plasma concentrations of trial drugs. RESULTS: No statistically significant treatment benefit effect was detected for tinnitus (intensity, pitch, and distress) VAS scores, arousal-anxiety VAS scores, Tinnitus Handicap Inventory, or tinnitus aggravation scores assessed on Days 1 and 14. However, a statistically significant worsening of tinnitus intensity and distress scores was observed after vestipitant compared with placebo for the mean data collected over the treatment period. No relevant differences in vestipitant plasma concentrations were observed between the subjects given the combination with paroxetine and those receiving vestipitant alone. No specific relationships were observed between tinnitus intensity and vestipitant plasma concentrations. CONCLUSION: Although well-tolerated vestipitant, alone or in combination with paroxetine, was not effective in ameliorating tinnitus in this patient group.

Radix Astragali injection enhances recovery from acute acoustic trauma.


Department of Otolaryngology.

Abstract Conclusion. The average recovery of hearing and cessation of tinnitus was significantly better after treatment with Radix Astragali (RA) than after non-treatment with RA. RA can be valuable adjuvant therapy for patients with acute acoustic trauma (AAT). Objectives. AAT is one of the early indications for the use of RA. The reasons for administering RA to patients with AAT are based on experimental studies showing that noise exposure results in the formation of reactive oxygen species (ROS), which trigger metabolic damage to the organ of Corti. RA is a natural antioxidant. The aim of this study was to investigate the efficacy of RA in patients with AAT. Methods: We compared the recovery from hearing impairment and tinnitus in 40 ears treated with RA with 40 ears treated with non-RA. RA was given intravenously daily for 10 days. There were no significant differences in clinical or audiological data between RA and non-RA groups. Results: The average recovery of hearing at both high and speech frequencies was significantly better and tinnitus persisted less commonly in the RA group than in the non-RA group. Normal hearing at the end of the follow-up period was regained in 27 ears in the RA group and in 21 ears in the non-RA group (p < 0.01).
Intratympanic Dexamethasone/Hyaluronic Acid Mix as an Adjunct to Intravenous Steroid and Vasoactive Treatment in Patients With Severe Idiopathic Sudden Sensorineural Hearing Loss. Otol Neurorol. 2011 Jun 3.

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OBJECTIVE: To evaluate differences in effectiveness (hearing recovery rates) between idiopathic sudden sensorineural hearing loss (ISSNHL) patients treated with intravenous therapy alone and patients treated with a combination of intravenous and intratympanic therapy. STUDY DESIGN: Retrospective case review. SETTING: Tertiary referral hospital center. PATIENTS AND INTERVENTIONS: Ninety-four patients with moderate ISSNHL treated with an intravenous steroid and vasoactive regimen (duration of therapy, 9 ± 2.76 d) and 76 patients with severe ISSNHL treated with a combination regimen of intravenous and intratympanic therapy (duration of therapy, 10 ± 2.71 d) were reviewed. In the latter patients' group, a series of 3 intratympanic injections of a dexamethasone/hyaluronic acid mix solution were applied every 2 days. MAIN OUTCOME MEASURE: Pure-tone audiometric thresholds at 0.5, 1, 2, 4, and 8 kHz were compared between groups using the Wilcoxon test. RESULTS: Combination therapy in severe ISSNHL did not show any statistically significant difference in effectiveness to intravenous therapy in moderate ISSNHL (p > 0.05). CONCLUSION: In patients with severe ISSNHL, starting intratympanic steroid therapy as an adjunct early in the course of intravenous steroid and vasoactive therapy improves hearing to a level which is obtained in patients with less severe (moderate) ISSNHL treated with intravenous therapy alone.


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OBJECTIVE: The purpose of this study was to determine, through a randomized, double-blind, placebo-controlled trial, whether intratympanic steroid injections (ITSI s) could improve hearing recovery in patients with sudden sensorineural hearing loss (SSHL) who did not respond to initial systemic steroid therapy. STUDY DESIGN: This was a prospective, randomized, double-blind, placebo-controlled study. SETTING: The study was conducted in 2 tertiary referral centers. PATIENTS: A total of 60 patients with idiopathic SSHL who did not respond to an initial round of systemic steroid therapy were included in this study. The subjects were randomized into an ITSI group and an intratympanic normal saline injection (ITNI) group, which were matched by age and sex. A total of 55 subjects completed the study. INTERVENTION: Participants received either ITSI s or ITNIs. Both groups received 4 injections within a 2-week period. MAIN OUTCOME MEASURES: Pure-tone thresholds were compared between the 2 groups 1 month after injection therapy. RESULTS: In the ITNI group, the pure-tone threshold was 69.9 ± 18.5 dB before intratympanic injection therapy. After therapy, the hearing threshold improved by an average of 4.5 ± 6.5 dB, and 10.7% of subjects improved by 10 dB or more. In the ITSI group, the pure-tone threshold was 64.6 ± 17.7 dB before intratympanic injection therapy. After the therapy, the hearing threshold improved by an average of 9.8 ± 8.5 dB, and 44.4% of subjects improved by 10 dB or more. Both the response rate and the level of hearing improvement were significantly greater in the ITSI group than in the ITNI group. CONCLUSION: These results demonstrate that ITSI s are beneficial as a salvage therapy for the treatment of patients with idiopathic SSHL who fail to respond to initial systemic steroid therapy.
The efficiency of intratympanic dexamethasone injection as a sequential treatment after initial systemic steroid therapy for sudden sensorineural hearing loss.

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The effect of intratympanic steroid injection is controversial as salvage or initial treatment option for sudden sensorineural hearing loss (SSNHL) and almost unknown if it is consecutively to use after initial systemic steroids. This study aimed to analyze the efficiency of intratympanic dexamethasone injection (ITDI) as a sequential treatment in the patients who failed initial systemic steroid treatments for SSNHL. Forty-six patients with SSNHL who did not respond to initial systemic steroids were prospectively included in the study. The patients were randomly classified into two groups; the ITDI group (21 patients) did not take four sequential ITDI within 2 weeks after systemic steroids, and the control group (25 patients) took any more medications. Hearing improvement was defined as a 10 dB or more decrease in the pure tone average (PTA) of the four-frequencies (0.5, 1, 2, and 3 kHz). Hearing improvement was observed in 10 (47.6%) of 21 ITDI patients and in 4 (16.0%) of 25 control patients (P = 0.027). An improvement of the mean PTA was 11.4 dB in the ITDI group and 1.7 dB in the control group (P = 0.004). The ITDI group showed significant hearing improvement at low frequency (500 Hz) than the control group. The patients with 70 or more dB in PTA before ITDI showed significant hearing improvement than the other patients with better PTAs (P = 0.038). The sequential ITDI, which is performed immediately after initial systemic steroid therapy, may be a simple, effective second-line treatment of choice for the patients who show poor response to initial treatments for SSNHL.

The Effect of Gabapentin on Gap Detection and Forward Masking in Young and Old Gerbils.
Ear Hear. 2011 Jul 1. [Epub ahead of print]

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OBJECTIVES: Auditory temporal processing frequently appears more affected in old subjects than would be predicted by the degree of peripheral hearing loss, pointing to an age-dependent central processing deficit. In parallel, an age-dependent decline of inhibitory function has been demonstrated in the auditory pathway, suggesting a causal relationship between temporal processing and inhibition. Gabapentin has been specifically synthesized as a potential gamma-amino-butyric-acid (GABA) mimetic with the capability to cross the blood-brain barrier. Gabapentin treatment ameliorated tinnitus in a rat model and improved tinnitus annoyance in humans with acoustic trauma. Consequently, the present study evaluated the effect of gabapentin on auditory temporal processing in the gerbil model.

DESIGN: Psychometric functions were collected for different test paradigms. (A) „Gap detection“: The detection of a gap in the middle of a 800 msec broadband noise pulse was determined either at 15 or at 30 dB SL. (B) „Forward masking“: The detection of a 20 msec probe stimulus following 2.5 msec after a 400 msec 40 dB SPL masker was determined with masker and probe frequency at 2.85 kHz. The effect of gabapentin was evaluated by collecting gap detection and forward masking functions before, during, and after treating gerbils with gabapentin doses of 115 or 350 mg/kg/day administered via drinking water. Data under different experimental conditions were collected for groups of 3 to 5 young (<2 years) and 6 to 10 old (>2 years) gerbils. Two-way analyses of variance for the factors age groups and treatment groups with subsequent pairwise comparisons for significant effects were used for the statistical evaluation of the data.

RESULTS: For gap detection, mean thresholds were significantly increased in the group of old as compared with the young gerbils at 30 dB SL (young 2.0 msec; old 3.2 msec) and at 15 dB SL (young 2.9 msec; old 9.1 msec). Gabapentin had no significant effect on gap detection, and there was no significant interaction between age group and gabapentin treatment. Mean thresholds in the forward masking paradigm were significantly elevated in old (45.5 dB SPL) as compared with young (35.0 dB
Overall, gabapentin had no significant effect on masked thresholds; however, there was a significant interaction between treatment and age. Subsequent pairwise comparisons revealed no significant effect on masked thresholds in old gerbils but showed significantly elevated thresholds of young gerbils during 350 mg/kg gabapentin (38.3 dB SPL) compared with thresholds obtained in young gerbils before (32.3 dB SPL) and after (33.5 dB SPL) treatment.

CONCLUSIONS: Gabapentin did not exert a therapeutic effect on impaired gap detection and forward masking in old gerbils. The lack of an effect of gabapentin on impaired auditory temporal processing in old gerbils and the finding of elevated masked thresholds in young gerbils can be reconciled with reports of only moderate GABAergic effects compared with other drugs (e.g., comparing elevation of GABA levels in the brain by gabapentin and vigabatrin) and effects due to binding of gabapentin to alpha-2-delta units of voltage-gated calcium channels.

Anticonvulsants for tinnitus.

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BACKGROUND: Tinnitus is the perception of sound or noise in the absence of an external or internal acoustic stimulation. It is a common and potentially distressing symptom for which no adequate therapy exists.

OBJECTIVES: To assess the effectiveness of anticonvulsants in patients with chronic tinnitus.

SEARCH STRATEGY: We searched the Cochrane Ear, Nose and Throat Disorders Group Specialised Register, CENTRAL (2010, Issue 2), MEDLINE, EMBASE, bibliographies and additional sources for published and unpublished trials. The date of the most recent search was 26 May 2010.

SELECTION CRITERIA: We selected randomised controlled trials in patients with chronic tinnitus comparing orally administered anticonvulsants with placebo. The primary outcome was improvement in tinnitus measured with validated questionnaires. Secondary outcomes were improvement in tinnitus measured with self-assessment scores, improvement in global well-being or accompanying symptoms, and adverse drug effects.

DATA COLLECTION AND ANALYSIS: Three authors assessed risk of bias and extracted data independently.

MAIN RESULTS: Seven trials (453 patients) were included in this review. These studies investigated four different anticonvulsants: gabapentin, carbamazepine, lamotrigine and flunarizine. The risk of bias of most studies was ‘high’ or ‘unclear’. Three studies included a validated questionnaire (primary outcome). None of them showed a significant positive effect of anticonvulsants. One study showed a significant negative effect of gabapentin compared to placebo with an increase in Tinnitus Questionnaire (TQ) score of 18.4 points (standardised mean difference (SMD) 0.82, 95% confidence interval (CI) 0.07 to 1.58). A second study showed a positive, non-significant effect of gabapentin with a difference compared to placebo of 2.4 points on the Tinnitus Handicap Inventory (THI) (SMD -0.11, 95% CI -0.48 to 0.25). When the data from these two studies are pooled no effect of gabapentin is found (SMD 0.07, 95% CI -0.26 to 0.40). A third study reported no differences on the THI after treatment with gabapentin compared to placebo (exact numbers could not be extracted from the article). A meta-analysis of ‘any positive effect’ (yes versus no) based on a self-assessment score (secondary outcome) showed a small favourable effect of anticonvulsants (RD 14%, 95% CI 6% to 22%). A meta-analysis of ‘near or total eradication of tinnitus annoyance’ showed no effect of anticonvulsants (risk difference (RD) 4%, 95% CI -2% to 11%). Side effects of the anticonvulsants used were experienced by 18% of patients.

AUTHORS’ CONCLUSIONS: Current evidence regarding the effectiveness of anticonvulsants in patients with tinnitus has significant risk of bias. There is no evidence from studies performed so far to show that anticonvulsants have a large positive effect in the treatment of tinnitus but a small effect (of doubtful clinical significance) has been demonstrated.
An in vitro model for testing drugs to treat tinnitus.
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Tinnitus affects approximately 50 million people in the USA alone, with 10 million being highly debilitated. Pharmacotherapy for tinnitus is still in emerging stages due to time consuming clinical trials and/or animal experiments. We tested a new cellular model where induced rapid neuronal firing or spiking was used as a mimic for the type of aberrant activity that may occur in tinnitus. Spontaneously active auditory cortical networks growing on microelectrode arrays were exposed to pentylenetetrazol (PTZ), a proconvulsant and an antagonist of GABA(A) receptor, which is implicated in tinnitus. Auditory cortical networks were then exposed to experimental tinnitus drugs linopirdine (Dup966, a potassium channel blocker), l-carnitine (an antioxidant), or selective Ca(2+) channel antagonists pregabalin (Lyrica), or gabapentin (Neurontin) at various concentrations. PTZ increased spike rate by 139.6±27% and burst rate by 129.7±28% in auditory cortical networks with a phenotypic high firing of excitable neurons. Reductions of increased activity were observed to varying degrees using the experimental tinnitus drugs. The potency of the drugs was linopirdine (EC(50): 176±7.0μM)>l-carnitine (EC(50): 1569±41μM)>pregabalin (EC(50): 8360±340μM), >gabapentin, with 34.2±7.5% efficacy (EC(50): 2092±980μM). These studies provide proof of principle for the use of auditory cortical networks on microelectrode array as a feasible platform for semi-high throughput application for screening of drugs that might be used for the treatment of tinnitus. Copyright © 2011 Elsevier B.V. All rights reserved.

Intratympanic steroids for Ménière's disease or syndrome.

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BACKGROUND: Ménière’s disease is a disorder characterised by hearing loss, tinnitus and disabling vertigo. The use of intratympanic steroids to reduce the severity of these symptoms has been gaining popularity. OBJECTIVES: To assess the effectiveness of intratympanic steroids on the frequency and severity of attacks of vertigo, on chronic symptoms such as tinnitus, imbalance and hearing loss, and on the progression of these symptoms in patients with definite Ménière’s disease or syndrome, as defined by the AAO-HNS Committee. SEARCH STRATEGY: We searched the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL); PubMed; EMBASE; CINAHL; Web of Science; BIOSIS Previews; Cambridge Scientific Abstracts; ICTRP and additional sources for published and unpublished trials. The date of the most recent search was 13 January 2011. SELECTION CRITERIA: Randomised controlled trials of intratympanic dexamethasone versus placebo in patients with Ménière’s disease. DATA COLLECTION AND ANALYSIS: Two authors independently assessed trial risk of bias and extracted data. We contacted study authors for further information where possible. MAIN RESULTS: A single trial containing 22 patients, with a low risk of bias was included. This trial found that after 24 months, compared with placebo, the use of intratympanic dexamethasone demonstrated a statistically significant improvement in vertigo as defined by a respective improvement in functional level (90% versus 42%), class (82% versus 57%), change in Dizziness Handicap Inventory scores (60.4 versus 41.3) and mean vertigo subjective improvement (90% versus 57%). The treatment regime described by the authors involved daily injections of dexamethasone solution 4 mg/ml for five consecutive days. These results were clinically significant. No complications were reported. AUTHORS’ CONCLUSIONS: The results of a single trial provide limited evidence to support the effectiveness of intratympanic steroids in patients with Ménière’s disease. This trial
demonstrated a statistically and clinically significant improvement of the frequency and severity of vertigo measured 24 months after the treatment was administered. It is important to note that there were a few aspects of the study which we were unable to clarify with the study authors.

VI Auditive Stimulation

Cochlear implantation as a durable tinnitus treatment in single-sided deafness.

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Introduction Severe tinnitus can seriously impair patients in their activities in daily life and reduce their quality of life. The aims of this prospective clinical study were to assess the long-term effects of cochlear implantation (CI) on tinnitus in patients with single-sided deafness and ipsilateral incapacitating tinnitus, and to investigate whether CI could treat various types of tinnitus. Materials and methods Twenty-six subjects with unilateral severe-to-profound sensorineural hearing loss received a CI. Patients suffered from severe tinnitus greater than 6/10 on a visual analogue scale (VAS) due to unilateral deafness. Assessment consisted of a tinnitus analysis including determination of tinnitus type, frequency, and loudness. A tinnitus questionnaire (TQ) measured tinnitus distress. VAS and TQ were administered pre-implantation and post-implantation. Results All 26 patients reported a subjective benefit from CI. Tinnitus loudness reduced significantly after CI from 8.6 to 2.2 on the VAS (scale: 0-10). The TQ total score decreased significantly and the mean tinnitus degree decreased from severe to mild. No differences were observed between patients with pure-tone tinnitus, narrow band noise tinnitus, or polyphonic tinnitus. The degree of tinnitus loudness reduction remained stable after CI. Conclusions CI can successfully be used as treatment of severe tinnitus in patients with single-sided deafness and is equally effective for pure tone, narrow band noise, and polyphonic tinnitus. Long-term results show that implantation provides durable tinnitus relief in these patients. These results support the hypothesis that physiopathological mechanisms after peripheral deafferentation are reversible when hearing is restored. Single-sided deafness accompanied by severe tinnitus is a new indication for CI.

The effects of unilateral cochlear implantation on the tinnitus handicap inventory and the influence on quality of life.

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Cochlear implantation is now the standard of care in patients with significant sensorineural hearing loss. It is well known that patients with severe hearing loss also experience disabling tinnitus. The purpose of this study was to assess the effects of cochlear implants on the perception of tinnitus using the Tinnitus Handicap Inventory (THI).
In recent years the indication criteria for cochlear implantation (CI) have changed. To gain optimal benefits, early implantation in prelingually deaf children is necessary. Even additional disabilities are no longer contraindications for CI. Nowadays the criteria for implantation not only include deafness but also residual hearing. Combined electric-acoustic stimulation has been established as a treatment option in patients with hearing still functioning in the low frequencies. Due to the benefits of binaural hearing, bilateral CI has become standard over the last decade. Recent experience has shown the benefits of CI in unilateral deafness and in cases of severe tinnitus. The actual benefit of CI shows great inter-individual differences. We usually expect (re-)habilitation of language communication skills with implantation.

Pitfalls in the management of monaural deafness.

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Objective: We report a patient who underwent cochlear implantation in an ear with long-term deafness, after an acoustic neuroma had been removed surgically from the other, hitherto good ear and the cochlear nerve had subsequently been resected to relieve severe tinnitus.

Method: Case report. Results: The patient could not tolerate the cochlear implant, because of a moderate headache due to the stimulation level necessary for environmental sound discrimination.

Conclusion: Cochlear implantation in patients with long-term deafness should be considered carefully, even if deafness is monaural.

Influence of tinnitus sound therapy signals on the intelligibility of speech.

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Objective: To assess the influence on speech intelligibility of various signals used in tinnitus sound therapy.

Materials and methods: We measured, in normal hearing subjects, the intelligibility of speech in the presence of three different sound therapy signals: wide-band noise, a recording of moving water, and a combination of tones.

Results: For a given level of stimulation, speech intelligibility was worst in the presence of wide-band noise, compared with the other sound therapy signals. When the stimulation level of the three different signals was increased, speech intelligibility deteriorated more rapidly with wide-band noise, compared with the other two signals. The combination of tones had the least influence on speech intelligibility.

Conclusion: The use of different tinnitus sound therapy signals can lead to significantly different effects on the intelligibility of speech. The use of natural sound recordings or combinations of tones may provide the patient with more flexibility to change the stimulation level during treatment.
Tinnitus retraining therapy using portable music players.

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OBJECTIVE: We aimed to perform acoustic analysis of environmental sounds used in sound therapy for tinnitus retraining therapy (TRT) and to evaluate the efficacy of TRT performed by using a portable music player (PMP) with recorded environmental sounds as the sound generator.

METHODS: Acoustic analysis of environmental sounds was performed using a sound analyzer. The subjects were 23 patients with chronic tinnitus. Patients who had bilateral hearing loss and required hearing assistance were fitted with hearing aids (HAs). Patients with normal hearing or unilateral hearing loss were fitted with a tinnitus control instrument (TCI) or a PMP. The patients were divided into the PMP group, TCI group, and HA group. All subjects underwent audiometric evaluations prior to TRT and completed the tinnitus handicap inventory (THI). The THI scores were evaluated before treatment and 1 month, 3 months, 6 months, and 12 months after treatment.

RESULTS: The sound spectrogram of the murmur of a stream showed a wide-frequency band with a constant strength, whereas that of a wave sound showed a wide-frequency band with variable strength. The THI score clearly decreased after 1 month, and this decrease tended to continue over 12 months. The TRT efficacy ratios in the PMP group, TCI group, and HA group at 12 months after treatment were 71%, 67%, and 70%, respectively.

CONCLUSIONS: TRT using a PMP had efficacy similar to those of TCI and HA. The murmur of a stream was one of the most effective sounds in TRT. TRT using a PMP as the sound generator can provide the most cost-effective treatment option for tinnitus patients. Copyright © 2011 Elsevier Ireland Ltd. All rights reserved.

Comparison of efficacy of different treatment methods in the treatment of idiopathic tinnitus.

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OBJECTIVES: This study aims to detect whether any differences were present between betahistine dihydrochloride, transcutaneous electrical nerve stimulation and pure tone masking-tinnitus retraining therapy (TRT) methods in the effects on quality of life and treatment of the symptoms of the patients.

PATIENTS AND METHODS: A total of 91 patients (42 females, 49 males; mean age 49.3±8.3 years; range 30 to 70 years) who admitted to the Otorhinolaryngology Clinic of the Ufuk University between June 2009 and June 2010 with a complaint of subjective tinnitus and who had no hearing loss were included in the study. In this study, the effects of these three treatment methods on healing and quality of life in patients suffering from bilateral subjective tinnitus were comparatively evaluated using Tinnitus Handicap Inventory Score (THIS), visual analog scale (VAS) and audiological parameters. The evaluations were made immediately before the treatment, immediately after the treatment and three weeks after the treatment. Kolmogorov-Smirnov analysis was used to test the normal distribution of the data and Wilcoxon signed rank test was used to show the differences between the different treatment methods before the treatment, immediately after the treatment and three weeks after the treatment. Mann-Whitney U and Kruskal-Wallis H tests were used to show the inter-group differences.

RESULTS: In the inter-group analyzes, success rate of the pure tone masking-TRT was much higher when compared to the other treatment methods. In the evaluations performed at the end of the three-month period, it was seen that the efficacy of the treatment was continuing.

CONCLUSION: According to these results, pure tone masking-TRT was found to be the best treatment method when compared to other methods and it was concluded that this treatment may be considered as the first choice in patients with idiopathic tinnitus.
Open ear hearing aids in tinnitus therapy: An efficacy comparison with sound generators.
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Parazzini M, Del Bo L, Jastreboff M, Tognola G, Ravazzani P.

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Abstract
Objective: This study aimed to compare the effectiveness of tinnitus retraining therapy (TRT) with sound generators or with open ear hearing aids in the rehabilitation of tinnitus for a group of subjects who, according to Jastreboff categories, can be treated with both approaches to sound therapy (borderline of Category 1 and 2). Design: This study was a prospective data collection with a parallel-group design which entailed that each subject was randomly assigned to one of the two treatments group: half of the subjects were fitted binaurally with sound generators, and the other half with open ear hearing aids. Both groups received the same educational counselling sessions. Study sample: Ninety-one subjects passed the screening criteria and were enrolled into the study. Structured interviews, with a variety of measures evaluated through the use of visual-analog scales and the tinnitus handicap inventory self-administered questionnaire, were performed before the therapy and at 3, 6, and 12 months during the therapy. Results: Data showed a highly significant improvement in both tinnitus treatments starting from the first three months and up to one year of therapy, with a progressive and statistically significant decrease in the disability every three months. Conclusions: TRT was equally effective with sound generator or open ear hearing aids: they gave basically identical, statistically indistinguishable results.

VII Brain Stimulation

Bifrontal transcranial direct current stimulation modulates tinnitus intensity and tinnitus-distress-related brain activity.

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Bifrontal transcranial direct current stimulation (tDCS), with the anodal electrode overlying the right and the cathodal electrode overlying the left dorsolateral prefrontal cortex, has been shown to suppress tinnitus significantly in 30% of patients. The source localized resting-state electrical activity is recorded before and after bifrontal tDCS in patients who respond to tDCS to unravel the mechanism by which tDCS suppresses tinnitus. The present electroencephalography study (N=12) provides support for the ability of bifrontal tDCS to suppress tinnitus intensity and tinnitus-related distress by modulation of the pregenual anterior cingulate cortex, parahippocampal area and right primary auditory cortex in resting-state spontaneous brain activity. These findings provide direct support for tDCS having an impact not only directly on the underlying dorsolateral prefrontal cortex but also indirectly on functionally connected brain areas relevant for tinnitus distress and tinnitus intensity, respectively. © 2011 The Authors. European Journal of Neuroscience © 2011 Federation of European Neuroscience Societies and Blackwell Publishing Ltd.
Treatment of chronic tinnitus with repeated sessions of prefrontal transcranial direct current stimulation: outcomes from an open-label pilot study.
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Tinnitus is the perception of sound in the absence of an environmental sound source. Abnormal activity in central auditory pathways is considered as the neuronal correlate of tinnitus. However, there is increasing evidence from neuroimaging studies for an additional involvement of the frontal cortex in the pathophysiology of tinnitus, especially concerning its attentional and emotional aspects. Recently, in a subgroup of tinnitus patients, temporary reduction of tinnitus intensity and tinnitus-related distress has been reported after bifrontal tDCS with the anode over the right and the cathode over the left dorsolateral prefrontal cortex (DLPFC). The aim of this study was to investigate whether repeated application of bifrontal tDCS results in longer-lasting reduction of tinnitus and may represent a potential treatment approach. Thirty-two patients with chronic and treatment-resistant tinnitus received six sessions of bifrontal tDCS (1.5 mA, 30 min, two sessions per week) with the anode over the right and the cathode over the left DLPFC. Treatment outcome was assessed with several standardized tinnitus questionnaires, numeric rating scales, and a depression scale. In the entire group, beneficial effects of bifrontal tDCS on tinnitus were found for numeric rating scores of loudness, unpleasantness, and discomfort, but not in tinnitus or depression scales. Exploratory analysis revealed an effect of gender on treatment effects with female patients demonstrating a better response in several scores. Our open-label pilot study suggests some beneficial effect of bifrontal tDCS (anode right and cathode left) in the treatment of severe tinnitus, warranting further controlled studies.

Short duration repetitive transcranial magnetic stimulation for tinnitus treatment: A prospective Asian study.
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BACKGROUND: Tinnitus is a subjective auditory perception of sounds or noise not triggered by external auditory stimuli. To date, treatment in severe cases is generally unsatisfactory. Characteristic functional brain imaging changes associated with tinnitus include hyperactivity encompassing both the primary auditory cortex (AC) and the secondary or associative cortex. Brief repetitive transcranial magnetic stimulation (rTMS) trains applied to the scalp overlying the hyperactive left AC is known to produce moderate tinnitus attenuation.

OBJECTIVE: Although Western studies have documented the value of rTMS in tinnitus treatment, we evaluate the efficacy of a short duration rTMS protocol for the first time in the Asian setting.

METHOD: Consecutive patients were recruited at our tinnitus clinic. Detailed history, examination, audiogram and baseline tinnitus scales were recorded. RTMS consisted of 1000 pulses/day at 1Hz and 110% of the motor threshold, for five consecutive days over the left temporoparietal cortex. Tinnitus ratings were determined weekly for 4 weeks after rTMS.

RESULT: Fifteen patients completed the trial; none experienced significant side effects. Repeated measures ANOVA showed significant linear decrease in Tinnitus Handicap Inventory (THI) scores over the time period (F((1,14))=4.7, p=0.04). However, none of the other parameters (severity, annoyance, effect on lifestyle and overall impression: visual analogue scale) showed beneficial outcomes.

CONCLUSIONS: Our findings point to a positive effect of short duration rTMS in tinnitus treatment using the THI. However, no significant benefits were demonstrated for other subjective patient ratings.
Although well tolerated and convenient, short duration rTMS may prove inadequate for modulating maladaptive plastic changes at the cortical level, and our results suggest the need for delivery of more stimuli. Future studies will utilize at least 2000 pulses/day, in line with previous experience in Western settings.

**Repetitive transcranial magnetic stimulation (rTMS) for treatment of chronic tinnitus.**


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**OBJECTIVE:** There is compelling evidence that tinnitus is associated with functional alterations in the central nervous system. Repetitive transcranial magnetic stimulation (rTMS) is a potent tool for modifying neural activity at the stimulated area and at a distance along the functional anatomical connections. Depending on the stimulation parameters, cortical networks can be functionally disturbed or modulated in their activities. Low-frequency rTMS has been shown to result in a decrease in cortical excitability. The technique can alleviate tinnitus by modulating the excitability of neurons in the auditory cortex. We aimed to investigate the effects of low-frequency rTMS in patients and determine the factors that predict a beneficial outcome with rTMS treatment.

**METHODS:** Sixteen patients (male 10, female 6) with chronic tinnitus underwent low-frequency (1Hz) rTMS (intensity: 110% motor threshold; number of stimuli: 1200) to the left auditory cortex. The treatment outcome was assessed with a visual analog scale (VAS) of loudness, annoyance and duration, loudness balance test, and tinnitus handicap inventory (THI). Therapeutic success was studied according to the patients’ clinical characteristics.

**RESULTS:** A significant reduction in the VAS (loudness and annoyance) occurred immediately after rTMS, with a gradual return to pretreatment levels after 7 days. The tinnitus patients with sudden deafness were significant resistant to rTMS treatment compared with those diagnosed with age-related hearing loss.

**CONCLUSION:** These results support the potential of rTMS as a new therapeutic tool for the treatment of chronic tinnitus. Because this study was performed with a small sample size and showed high interindividual variability in treatment effects, further development of the technique is needed before it can be recommended for clinical applications.

**Vagus nerve stimulation modulates cortical synchrony and excitability through the activation of muscarinic receptors.**
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Vagus nerve stimulation (VNS) is an FDA approved treatment for drug-resistant epilepsy and depression. Recently, we demonstrated the capacity for repeatedly pairing sensory input with brief pulses of VNS to induce input specific reorganization in rat auditory cortex. This was subsequently used to reverse the pathological neural and perceptual correlates of hearing loss induced tinnitus. Despite its therapeutic potential, VNS mechanisms of action remain speculative. In this study, we report the acute effects of VNS on intra-cortical synchrony, excitability, and sensory processing in anesthetized rat auditory cortex. VNS significantly increased and decorrelated spontaneous multi-unit activity, and suppressed entrainment to repetitive noise burst stimulation at 6-8 Hz but not after application of the muscarinic antagonist scopolamine. Collectively, these experiments demonstrate the capacity for VNS to acutely influence cortical synchrony and excitability and strengthen the hypothesis that acetylcholine and
muscarinic receptors are involved in VNS mechanisms of action. These results are discussed with respect to their possible implications for sensory processing, neural plasticity, and epilepsy. Copyright © 2011. Published by Elsevier Ltd.

VIII Behavioral Therapy

A systematic review and meta-analysis of randomized controlled trials of cognitive-behavioral therapy for tinnitus distress.

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Tinnitus is defined as a sound in the ear(s) and/or head without external origin and is a serious health concern for millions worldwide. The aim of the present study was to determine whether Cognitive Behavior Therapy (CBT) is effective in reducing distress associated with tinnitus. Randomized, controlled trials that assessed the efficacy of CBT for tinnitus-related distress in adults were identified by searching electronic databases (PsychINFO, PubMed, the Cochrane Library), and by manual searches. Fifteen studies (total of 1091 participants) were included in the meta-analysis. CBT compared with a passive and active control at post-assessment yielded statistically significant mean effect sizes for tinnitus-specific measures (Hedges’s g=0.70, and Hedges’s g=0.44, respectively). The average weighted pre-to-follow-up effect size for the CBT group suggested that these effects were maintained over time. Smaller but yet statistically significant effects of CBT were found for mood outcome measures. Characteristics of the studies were unrelated to effect sizes. Methodological rigor, publication bias, and a series of sensitivity analyses did not influence the findings. The results suggest that CBT is an effective treatment of tinnitus distress. However, caution is warranted given that few large-scale, well-controlled trials were identified.

Neurofeedback for subjective tinnitus patients.

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OBJECTIVE: Previous studies report that enhanced power in the delta range (1.5-4Hz) and reduced power in the alpha frequency band (8-12Hz) were most pronounced in the temporal regions. These studies referred to the 8-12Hz activity as tau activity, and they created a new neurofeedback protocol to treat tinnitus using a temporally generated tau rhythm (8-12Hz) and slow waves in the delta range (3-4Hz) for feedback. This study aims to repeat this protocol and to evaluate its effect on tinnitus. METHODS: Fifteen normal-hearing patients with tinnitus were treated with the neurofeedback protocol. The Tinnitus Handicap Inventory and Visual Analogue Scales were administered before and after treatment and at 1, 3 and 6 months post-treatment. RESULTS: After therapy, all questionnaires scores were significant improved, and the improvements persisted throughout the followup period. Moreover, an increasing trend in the tau/delta ratio was observed; specifically, the trend was more stable respect of the pre-recording measure. However, only in some subjects may the signal alone be enough to develop the correct behaviors. CONCLUSION: Further studies are necessary to characterize the tinnitus subjects who recovered from and adapted to this psychophysical condition and, therefore, responded to neurofeedback therapy. Copyright © 2011 Elsevier Ireland Ltd. All rights reserved.
A Randomized Controlled Trial of Mindfulness-Based Cognitive Therapy for Treating Tinnitus.

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We conducted a randomized clinical trial to examine the relative effectiveness of two psychological interventions for treating tinnitus. People with tinnitus were initially offered a single session of psychoeducation about tinnitus, followed 2 months later by six weekly sessions of either mindfulness or relaxation training. Results indicated benefits from psychoeducation in reducing negative emotions, rumination and psychological difficulties of living with tinnitus. These effects were maintained or enhanced by mindfulness training that also emphasized acceptance, although they were eroded in the relaxation condition over the follow-up. Mediating processes are discussed, and suggestions for refining clinical interventions for this population are offered. Copyright © 2011 John Wiley & Sons, Ltd. KEY PRACTITIONER MESSAGE: The present results suggest that mindfulness training might constitute a useful addition to psychoeducation for interventions targeting the psychological consequences of tinnitus. Copyright © 2011 John Wiley & Sons, Ltd.

IX Somatic Tinnitus

Tinnitus with Temporomandibular Joint Disorders: A Specific Entity of Tinnitus Patients?

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Objective. Tinnitus is frequently associated with temporomandibular joint (TMJ) dysfunction. However, the nature of the relationship is not fully understood. Here the authors compared 30 patients with a confirmed diagnosis of temporomandibular joint dysfunction and tinnitus to a group of 61 patients with tinnitus but without any subjective complaints of TMJ dysfunction with respect to clinical and demographic characteristics. Study Design. Case-control study. Setting. Tertiary referral center. Subjects. Tinnitus patients with and without TMJ dysfunction presenting at the Department of Prosthetic Dentistry and the Tinnitus Clinic at the University of Regensburg. Results. Tinnitus patients with TMJ disorder had better hearing function (P < .0005), lower age (P = .001), and lower age at tinnitus onset (P = .002) and were more frequently female (P = .003). Their subjectively perceived tinnitus loudness was lower (P = .01), and more of them could modulate their tinnitus by jaw or neck movements (P = .001). Conclusion. Classical risk factors for tinnitus (age, male gender, hearing loss) are less relevant in tinnitus patients with TMJ disorder, suggesting a causal role of TMJ pathology in the generation and maintenance of tinnitus. Based on this finding, treatment of TMJ disorder may represent a causally oriented treatment strategy for tinnitus.

Plasticity of somatosensory inputs to the cochlear nucleus - Implications for tinnitus.
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This chapter reviews evidence for functional connections of the somatosensory and auditory systems at the very lowest levels of the nervous system. Neural inputs from the dosal root and trigeminal ganglia, as well as their brain stem nuclei, cuneate, gracilis and trigeminal, terminate in the cochlear nuclei. Terminations are primarily in the shell regions surrounding the cochlear nuclei but some terminals
are found in the magnocellular regions of cochlear nucleus. The effects of stimulating these inputs on multisensory integration are shown as short and long-term, both suppressive and enhancing. Evidence that these projections are glutamatergic and are altered after cochlear damage is provided in the light of probable influences on the modulation and generation of tinnitus. Copyright © 2011 Elsevier B.V. All rights reserved.

**Medio-lateral postural instability in subjects with tinnitus.**

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Background: Many patients show modulation of tinnitus by gaze, jaw or neck movements, reflecting abnormal sensorimotor integration, and interaction between various inputs. Postural control is based on multi-sensory integration (visual, vestibular, somatosensory, and oculomotor) and indeed there is now evidence that posture can also be influenced by sound. Perhaps tinnitus influences posture similarly to external sound. This study examines the quality of postural performance in quiet stance in patients with modulated tinnitus.

**Methods:** Twenty-three patients with highly modulated tinnitus were selected in the ENT service. Twelve reported exclusively or predominately left tinnitus, eight right, and three bilateral. Eighteen control subjects were also tested. Subjects were asked to fixate a target at 40 cm for 51 s; posturography was performed with the platform (Technoconcept, 40 Hz) for both the eyes open and eyes closed conditions.

**Results:** For both conditions, tinnitus subjects showed abnormally high lateral body sway (SDx). This was corroborated by fast Fourier Transformation (FFTx) and wavelet analysis. For patients with left tinnitus only, medio-lateral sway increased significantly when looking away from the center.

**Conclusion:** Similarly to external sound stimulation, tinnitus could influence lateral sway by activating attention shift, and perhaps vestibular responses. Poor integration of sensorimotor signals is another possibility. Such abnormalities would be accentuated in left tinnitus because of the importance of the right cerebral cortex in processing both auditory-tinnitus eye position and attention.

**Auriculo-vestibular symptoms related to structural and functional disorders of stomatognatic system.**

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Auriculo-vestibular symptoms are otolaryngological complaints which frequently co-occur with functional disorders of masticatory organ. These symptoms include: earache, plugged ears sensation, sudden hearing impairment, burning pain of the throat, tinnitus, and dizziness. The aim of the study was assessment of co-occurrence of functional disorders of masticatory organ and auriculo-vestibular symptoms, in patients referred for otolaryngological treatment. Forty-two patients aged 24-46 years of both sexes referred for otolaryngological treatment, because of auriculo-vestibular symptoms, were qualified to our study within the framework of research project. After otolaryngological diagnostics (Department of Otolaryngology), these patients were referred for prosthetic consultation to the Department of Dental Prosthetics of Jagiellonian University Medical College. In Otolaryngology Clinic the following specialist examinations were carried out: basic clinical examinations, including otoscopy, tuning fork trials, tonal and verbal audiometry, and tympanometry. These examinations were supplemented with electronystagmometry. On prosthetic consultation, specialist functional investigations of masticatory organ, and electromyographic assessment of the activity of masseter muscles and the anterior part of the temporal muscle, were carried out. Results of the investigation revealed otolaryngological causes of the reported symptoms in 30 patients, whereas in 12 patients (out of 42 patients referred for
prosthetic consultation), numerous functional disorders of the stomatognathic system were observed. The investigation confirmed the occurrence of functional disorders in patients with auriculo-vestibular symptoms and appropriateness of treatment by a multi-specialist team.

**X Surgical Treatment**

**Sinus Wall Reconstruction for Sigmoid Sinus Diverticulum and Dehiscence: A Standardized Surgical Procedure for a Range of Radiographic Findings.**


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OBJECTIVE: To describe the radiographic presentation, surgical treatment, and complications of pulse-synchronous tinnitus (PST) due to sigmoid sinus diverticulum and dehiscence.

STUDY DESIGN: Retrospective case series.

SETTING: Tertiary care, academic medical center.

PATIENTS: Thirteen patients (14 ears) surgically treated for PST due to sigmoid sinus diverticulum and dehiscence.

INTERVENTION: Transmastoid reconstruction of the sinus wall with a standardized technique.

MAIN OUTCOME MEASURE: Resolution of PST and complications of surgery.

RESULTS: All patients had complete resolution of their PST after surgery. There were 2 major postoperative complications, neither of which resulted in permanent morbidity.

CONCLUSION: Sigmoid sinus diverticulum and dehiscence is a surgically treatable cause of PST, with a high rate of success. The radiographic diagnosis may be subtle and easily overlooked. Complications of surgery can be serious, and vigilance must be maintained to ensure prompt diagnosis and treatment.

**Gamma knife radiosurgery for vestibular schwannomas: tumor control and functional preservation in 70 patients.**


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OBJECTIVE: We present the previously unreported outcomes of 70 patients treated with Gamma knife radiosurgery for vestibular schwannoma (VS), including comprehensive analysis of clinical outcomes and the effects of lower marginal doses.

METHODS: We performed a retrospective study of patients treated for VS at Gamma knife of Spokane between 2003 and 2008. Endpoints measured include tumor control, hearing preservation, and facial nerve preservation, including the effect of tumor size and marginal dose. Statistical analysis was performed with Wilcoxon signed-rank test, paired Student t test, Mann-Whitney U test, Kendall's rank correlation, Fisher exact test, and Liddell's exact \( \chi^2 \) test for matched pairs.

RESULTS: With a mean follow-up of 26 months, 93.8% of tumors either shrank or remained static after receiving a mean marginal dose of 12.7 Gy. Tumor control was independent of marginal dose or tumor size. Hearing preservation was achieved in 64% of patients with serviceable function before the treatment. Hearing changes were independent of dose or tumor size. Preservation of good facial nerve function was achieved in 95% of patients. Post-treatment hydrocephalus occurred in 4.4% of patients, but no other significant morbidities were elucidated.

CONCLUSIONS: In the treatment of VS, contemporary radiosurgical techniques and the use of marginal doses below 13 Gy offer excellent tumor control, at high rates relative to surgical intervention. These findings are independent of marginal dose and tumor size. Patients should be informed about the
benefits and risks of radiosurgery and microsurgery before choosing an intervention. Further analysis of post-treatment outcomes should be encouraged as follow-up times increase and the treatment protocols continue to evolve.

Management of Vagal Paragangliomas Including Application of Internal Carotid Artery Stenting. A bold

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Background: The primary treatment of vagal paraganglioma (VP) includes ‘wait and scan’, surgery and radiotherapy. Objectives: To present the clinical findings, surgical treatment including application of internal carotid artery (ICA) stenting to facilitate surgery, and complications, as well as to review the literature and to discuss the decision-making process in the management of VP cases based on our experience and the literature. Design: A retrospective case review of 22 cases with VP. Setting: Quaternary neurotologic and skull base referral center. Material and Methods: The retrospective chart review identified 22 patients presenting with VP. Our indication for surgery was VP in younger patients, irrespective of the existence of vocal cord paralysis. Preoperative endovascular management of the ICA included permanent balloon occlusion (PBO) and stenting. The transcervical approach and the infratemporal fossa approach type A (ITFA) were used. Results: Fifteen cases had multicentric paragangliomas, 5 cases bilateral tumors, 3 cases a genetic mutation, and 2 cases a positive family history. The most common symptoms were hoarseness, tinnitus and hearing loss. The surgical approaches commonly employed for excision were the transcervical approach (9 cases) and the ITFA (12 cases), whereas 1 case did not have surgery. Three cases had PBO and 7 had intracarotid stent insertion. Gross total removal was achieved in 19 cases, and 1 case had a recurrence. Eighteen cases had no dysphagia or were well compensated after surgery. There were no significant complications noted in our series. Conclusions: In younger patients with VP, surgery should be recommended. The proper preoperative endovascular intervention and surgical approach facilitates gross total tumor removal. In the management of bilateral or familial paragangliomas, careful and appropriate decision making is essential.

Transmastoid Middle Fossa Craniotomy Repair of Superior Semicircular Canal Dehiscence Using a Soft Tissue Graft.


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OBJECTIVE: To describe the successful surgical treatment of 5 cases of superior semicircular canal dehiscence via a transmastoid middle fossa craniotomy using a soft tissue graft. DESIGN: Case report. SETTING: Private practice otologic referral center. RESULTS: All patients have experienced reduction in auditory and vestibular symptoms. Pulsatile tinnitus and autophony are now absent in the operated ears. Chronic disequilibrium is subjectively improved. Patients with sound evoked eye movements no longer have sound sensitivity on the operated side. Head thrust testing indicates no obstruction of the operated superior canal in all patients with normal head thrust preoperatively. Audiometry is unchanged from preoperation, and cervical vestibular-evoked myogenic potential thresholds have increased on the operated side in 4 of 4 patients. Three patients had dehiscence at the superior petrosal sinus inaccessible to standard middle fossa repair. All patients were discharged to home the morning after
surgery. CONCLUSION: Transmastoid craniotomy repair of the superior semicircular canal dehiscence using a soft tissue graft offers numerous advantages over traditional surgical approaches and can be performed safely in the outpatient setting. The strategy is particularly useful in patients with dehiscence at the superior petrosal sinus. This article will review our strategy and discuss the advantages and disadvantages of the different surgical treatments used for patients with severe symptoms from superior canal dehiscence.


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The role of endovascular interventions in managing dural arteriovenous fistulas (DAVFs) is increasing. Furthermore, in patients with aggressive DAVFs, different surgical interventions are required for complete obliteration or disconnection. Our objective was to evaluate the management of patients with intracranial DAVFs treated in our institution to identify the parameters that may help guide the long-term management of these lesions.

Tympanotomy and sealing of the round window for treatment of sudden deafness.

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INTRODUCTION: The objective of this study was to evaluate the effectiveness of explorative tympanotomy and sealing of the round window in patients diagnosed with sudden deafness. MATERIAL AND METHODS: A retrospective study of 22 patients presenting with sudden deafness who were treated with exploratory tympanotomy and sealing of the round window. The patients initially received conservative therapy for one month. If conservative treatment had no effect, exploratory tympanotomy and sealing of the round window was performed. RESULTS: The median pure tone average was 67 dB before surgery. Post-operatively, it was reduced to 55 dB. This is equivalent to a 12 dB (p = 0.008) improvement. Five patients improved beyond 30 dB and three patients out of 22 fulfilled the Belfast criteria for binaural hearing at the end of the observation period. Furthermore, three months after surgery, the incidence of vertigo and tinnitus had decreased from 58% to 8% and from 50% to 17%, respectively (p < 0.001 and p = 0.04). None of the patients experienced any severe or life-threatening complications. CONCLUSION: The results suggest that explorative tympanotomy and sealing of the round window may improve hearing and reduce tinnitus and vertigo after spontaneous remission has come to an end. However, randomized controlled studies are needed.
Post-operative complications after removal of sporadic vestibular schwannoma via retrosigmoid-suboccipital approach: current diagnosis and management.

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The retrosigmoid (suboccipital) approach is one of four surgical approaches for the treatment of vestibular schwannomas (acoustic neuromas). It is increasingly used by otologic surgeons, and in experienced hands is associated with improved results and more limited complications. Mortality rates are minimal and often zero, while postoperative sequelae, on the other hand, are not rare. In order to not only save the patient's life, but also to assure good quality of life after the surgery, one must consider many different aspects of management of the respective complications. In this review the issues of current management of CSF leak and meningitis, facial paresis, headache, hearing loss, unsteadiness, disequilibrium, vertigo, tinnitus, cerebellar and brain stem injuries or abscess, vascular complications and venous air embolism after retrosigmoid approach for removal of vestibular schwannomas are presented. © Springer-Verlag 2011

XI Holistic

no publications this time

XII Review

Pharmacological drugs inducing ototoxicity, vestibular symptoms and tinnitus: a reasoned and updated guide.

Cianfrone G, Pentangelo D, Cianfrone E, Mazzei F, Turchetta R, Orlando MP, Altissimi G.

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The present work on drug-induced ototoxicity, tinnitus and vertigo represents the update and revision of a previous guide to adverse drug reactions for Italian physicians (2005). The panorama of drug-induced side effects causing ototoxicity or symptoms such as tinnitus or dizziness and vertigo has enlarged in recent years, thanks to a better knowledge and a more specific attention of pharmaceutical firms and drug-control institutions. In daily clinical practice, there is a need for the family physician and the ENT specialist or audiologist (also in consideration of the possible medico-legal implications) to focus the attention on the possible risk of otological side effects. This would allow a clinical risk-benefit evaluation, weighing the possible clinical advantage in their field of competence against possible otological side-effects. The list of active ingredients and drugs is subdivided in categories based on their audiological and otoneurological side-effects, that have been signaled by the drug companies and/or ministerial notes. Drugs have also been subcategorized with regards to the field in which they are applied, the therapeutic indications and the clinical behaviour. They have also been organized in alphabetical order, for an easier consultation. The guide above, even if initially conceived for being used in Italy, also presents a more general and international interest, especially as for as the concepts of pharmacology and the features of the active ingredients are concerned. The guide is, therefore, useful as for as we are concerned to any physician, regardless of the country he/she operates in.
A review of tinnitus symptoms beyond 'ringing in the ears': a call to action.

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Abstract Background: Tinnitus, often referred to as 'ringing in the ears', is highly prevalent. However, patients may also present with a number of other symptoms. Scope: To review the broad range of symptoms of tinnitus, to evaluate their impact on patient quality of life and to explore methods of diagnosis and assessment. An electronic literature search was performed in PubMed between September and December 2010. Findings: Accumulating evidence suggests that the symptoms of tinnitus are not confined to the characteristic 'ringing in the ears', but instead encompass wide-ranging symptoms that include emotional components such as sleep disturbance, anxiety, depression, irritation, and concentration difficulties. Conclusion: Patients with tinnitus experience a spectrum of distressing symptoms that impact their quality of life and there is a clear need for action. Clinicians need to recognize and diagnose tinnitus that occurs with other wide-ranging symptoms to ensure that these symptoms are identified and patients receive effective treatment.

Tinnitus: Models and mechanisms.

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Over the past decade, there has been a burgeoning of scientific interest in the neurobiological origins of tinnitus. During this period, numerous behavioral and physiological animal models have been developed which have yielded major clues concerning the likely neural correlates of acute and chronic forms of tinnitus and the processes leading to their induction. The data increasingly converge on the view that tinnitus is a systemic problem stemming from imbalances in the excitatory and inhibitory inputs to auditory neurons. Such changes occur at multiple levels of the auditory system and involve a combination of interacting phenomena that are triggered by loss of normal input from the inner ear. This loss sets in motion a number of plastic readjustments in the central auditory system and sometimes beyond the auditory system that culminate in the induction of aberrant states of activation that include hyperactivity, bursting discharges and increases in neural synchrony. This article will review what has been learned about the biological origins of these alterations, summarize where they occur and examine the cellular and molecular mechanisms that are most likely to underlie them.

Alpha rhythms in audition: cognitive and clinical perspectives.

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Like the visual and the sensorimotor systems, the auditory system exhibits pronounced alpha-like resting oscillatory activity. Due to the relatively small spatial extent of auditory cortical areas, this rhythmic activity is less obvious and frequently masked by non-auditory alpha-generators when recording non-invasively using magnetoencephalography (MEG) or electroencephalography (EEG). Following stimulation with sounds, marked desynchronizations can be observed between 6 and 12Hz, which can be localized to the auditory cortex. However knowledge about the functional relevance of the auditory alpha rhythm has remained scarce so far. Results from the visual and sensorimotor system have fuelled the hypothesis of alpha activity reflecting a state of functional inhibition. The current article pursues several intentions: (1) Firstly we review and present own evidence (MEG, EEG, sEEG) for the
existence of an auditory alpha-like rhythm independent of visual or motor generators, something that is occasionally met with skepticism. (2) In a second part we will discuss tinnitus and how this audiological symptom may relate to reduced background alpha. The clinical part will give an introduction into a method which aims to modulate neurophysiological activity hypothesized to underlie this distressing disorder. Using neurofeedback, one is able to directly target relevant oscillatory activity. Preliminary data point to a high potential of this approach for treating tinnitus. (3) Finally, in a cognitive neuroscientific part we will show that auditory alpha is modulated by anticipation/expectations with and without auditory stimulation. We will also introduce ideas and initial evidence that alpha oscillations are involved in the most complex capability of the auditory system, namely speech perception. The evidence presented in this article corroborates findings from other modalities, indicating that alpha-like activity functionally has an universal inhibitory role across sensory modalities.

**Tinnitus and depression.**

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Abstract Objectives. Depressive symptoms are common in individuals with tinnitus and may substantially aggravate their distress. The mechanisms, however, by which depression and tinnitus mutually interact are still not fully understood. Methods. Here we review neurobiological knowledge relevant for the interplay between depression and tinnitus. Results. Neuroimaging studies confirm the existence of neural circuits that are activated both in depression and tinnitus. Studies of neuroendocrine function demonstrate alterations of the HPA-axis in depression and, more recently, in tinnitus. Studies addressing neurotransmission suggest that the dorsal cochlear nucleus that is typically hyperactive in tinnitus, is also involved in the control of attention and emotional responses via projections to the locus coeruleus, the reticular formation and the raphe nuclei. Impaired hippocampal neurogenesis has been documented in animals with tinnitus after noise trauma, as in animal models of depression. Finally, from investigations of human candidate genes, there is some evidence to suggest that variant BDNF may act as a common susceptibility factor in both disorders. Conclusions. These parallels in the pathophysiology of tinnitus and depression argue against comorbidity by chance and against depression as pure reaction on tinnitus. Instead, they stand for a complex interplay between tinnitus and depression. Implications for tinnitus treatment are discussed.

**Systematic review and meta-analyses of randomized controlled trials examining tinnitus management.**

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OBJECTIVES/HYPOTHESIS: To evaluate the existing level of evidence for tinnitus management strategies identified in the UK Department of Health’s Good Practice Guideline. STUDY DESIGN: Systematic review of peer-reviewed literature and meta-analyses. METHODS: Searches were conducted in PubMed, Cambridge Scientific Abstracts, Web of Science, and EMBASE (earliest to August 2010), supplemented by hand searches in October 2010. Only randomized controlled trials that used validated questionnaire measures of symptoms (i.e., measures of tinnitus distress, anxiety, depression) were included. RESULTS: Twenty-eight randomized controlled trials met our inclusion criteria, most of which provide moderate levels of evidence for the effects they reported. Levels of evidence were generally limited by the lack of blinding, lack of power calculations, and incomplete data reporting in these studies. Only studies examining cognitive behavioral therapy were numerous and similar enough to perform meta-analysis, from which the efficacy of cognitive behavioral therapy (moderate effect size)
appears to be reasonably established. Antidepressants were the only drug class to show any evidence of potential benefit. CONCLUSIONS: The efficacy of most interventions for tinnitus benefit remains to be demonstrated conclusively. In particular, high-level assessment of the benefit derived from those interventions most commonly used in practice, namely hearing aids, maskers, and tinnitus retraining therapy needs to be performed. Copyright © 2011 The American Laryngological, Rhinological, and Otological Society, Inc.

XIII Others

The Otology Data Collection Project: Report from the CHEER Network.

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Objective. To describe and communicate data collected in the CHEER (Creating Healthcare Excellence through Education and Research) infrastructure proof-of-concept study to facilitate understanding of the potential capabilities of practice-based research networks and to present pilot data for development of future research initiatives. Study Design. Prospective observational study of CHEER infrastructure operational capacity using a convenience sample of all patients presenting to the practices with tinnitus, dizziness, or a combination of these symptoms. Setting. The CHEER network of community and academic practice sites. Subjects and Methods. The data collection exercise collected demographic, clinical, treatment, and health-related quality-of-life surveys on tinnitus, dizziness, and migraine disorders. Descriptive analysis of the data is presented. Results. Of the sites in the CHEER network, 73% (16/22) successfully enrolled subjects; a total of 1532 patients were enrolled in 8 months. Tinnitus alone, dizziness alone, and both occurred in 28%, 34%, and 29%, respectively. Patients complaining of tinnitus and dizziness had lower quality of life than those sufferers with 1 disorder. Migraine was associated with 27% of patients. The most frequent diagnoses for patients with tinnitus and dizziness were Ménière disease (34%), vertiginous migraine (18%), and benign paroxysmal positional vertigo (16%). Conclusion. Descriptive data on patients with common disorders can be rapidly collected within the framework of a practice-based research network. The data in this study provide valuable pilot information on the targeted disorders, providing a baseline for development of future epidemiological data and clinical trials.

The comparison of acoustic and psychic parameters of subjective tinnitus.
Eur Arch Otorhinolaryngol. 2011 Jun 3;

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We aim to assess the correlation between audiometric data, and psychotic and acoustic measures associated with subjective tinnitus (ST) and to clarify the importance of the psychological process in determining the degree of subjective annoyance and disability due to tinnitus. Fifty-four patients experiencing unilateral ST were allocated for the study. Acoustic assessment of patients including LDL (loudness discomfort levels), MML (minimum masking level) and RI (residual inhibition) was performed. Tinnitus Handicap Inventory (THI), Beck Depression Inventory (BDI) and Visual Analog Scale (VAS) tests were performed for the psychological aspects of subjective annoyance. RI was positive in 23 patients with 13 frequency-matched stimuli at 8,000 Hz. Masking treatment response was successful in 16 RI-positive patients. Mean and standard deviation (SD) of THI scores were 38.77 ± 23.63. Ten patients (%18.51) with tinnitus had ≥17 points score, which was significant for BDI. Mean and SD were 5.01 ± 2.31 for VAS-1 scores (severity of tinnitus), 7.98 ± 2.79 for VAS-2 (frequency and duration of tinnitus), 5.77 ± 2.72 for VAS-3 (discomfort level), 3.56 ± 3.30 for VAS-4 (attention deficit) and 3.31 ± 3.31 for
VAS-5 (sleep disorders). A significant correlation was found between the tinnitus duration time, age, gender and THI scores (P < 0.05). There were statistically significant correlations between VAS 1, 2, 3 scores and LDL, MML and RI (P > 0.05). RI might be largely frequency dependent and was found as an indicator for the masking treatment response. We did not notice statistically significant correlations between audiometric data and THI and BDI. There were correlations between with VAS and LDL and with MML and RI. VAS was simpler and easier for the assessment of ST. We should consider the psychological aspects of ST and assess it as a symptom separately with acoustic and psychotic tests.

Primary care for tinnitus: practice and opinion among GPs in England.


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Effective tinnitus management starts with Rationale, aim and objective appropriate general practitioner (GP) triage, which in England can be guided by the Department of Health’s Good Practice Guide (GPG). Despite the prevalence of the condition, there has never been a systematic survey of its management in primary care in England. We aimed to evaluate how people with tinnitus are assessed and managed in general practice, noting variation in practice across GPs and health authorities, and evaluating how closely typical practice aligns. A nine-item postal questionnaire was sent to to the GPG for tinnitus. Methods GPs randomly selected to proportionally represent the number of primary 2000 care trusts and strategic health authorities in England. Results 368 responses. Responses indicated a mix of frequent and infrequent practices, for example, 90% of GPs assessed the impact of tinnitus on quality of life, but fewer examined cranial nerves (38%) or assessed for a carotid bruit (26%) during a tinnitus consultation. In the management of tinnitus, 83% routinely removed earwax, and 87% provided information-based advice. In contrast, only 4% of responders would offer antidepressant drugs or psychological therapies. Thematic analysis revealed a desire for concise training on tinnitus management. GP assessment and management of tinnitus represents potential inequity of service for tinnitus patients. While the GPG aims to promote equity of care, it is only referred to by a minority of clinicians and so its utility for guiding service delivery is questionable. Although some GPs highlighted little demand for tinnitus management within their practice, many others expressed an unmet need for specific and concise GP training on tinnitus management. Further work should therefore evaluate current informational resources and propose effective modes of delivering educational updates.

Tinnitus referral pathways within the National Health Service in England: a survey of their perceived effectiveness among audiology staff.
BMC Health Serv Res. 2011 Jul 6;11(1):162. [Epub ahead of print]

Gander PE, Hoare DJ, Collins L, Smith S, Hall DA.

BACKGROUND: In the UK, audiology services deliver the majority of tinnitus patient care, but not all patients experience the same level of service. In 2009, the Department of Health released a Good Practice Guide to inform commissioners about key aspects of a quality tinnitus service in order to promote equity of tinnitus patient care in UK primary care, audiology, and in specialist multi-disciplinary centres. The purpose of the present research was to evaluate utilisation and opinions on pathways for the referral of tinnitus patients to and from English Audiology Departments. METHODS: We surveyed all audiology staff engaged in providing tinnitus services across England. A 36-item questionnaire was mailed to 351 clinicians in all 163 National Health Service (NHS) Trusts identified
as having a tinnitus service. 138 clinicians responded. The results presented here describe experiences and opinions of the current patient pathways to and from the audiology tinnitus service.

RESULTS: The most common referral pathway was from general practice to a hospital-based Ear, Nose & Throat department and from there to a hospital-based audiology department (64%). Respondents considered the NHS tinnitus referral process to be generally effective (67%), but expressed needs for improving GP referral and patients' access to services. ‘Open access’ to the audiology clinic was rarely an option for patients (9%), nor was the opportunity to access specialist counselling provided by clinical psychology (35%). To decrease the number of inappropriate referrals, 40% of respondents called for greater awareness by referrers about the audiology tinnitus service.

CONCLUSIONS: Respondents in the present survey were generally satisfied with the tinnitus referral system. However, they highlighted some potential targets for service improvement including (1) faster and more appropriate referral from GPs, to be achieved through education on tinnitus referral criteria, (2) improved access to psychological services through audiologist training, and (3) ongoing support from tinnitus support groups, national charities, or open access to the tinnitus clinic for existing patients.

Implementation and Testing of Research Infrastructure for Practice-Based Research in Hearing and Communication Disorders.

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Objective. To describe site capability and experience of the CHEER network (Creating Healthcare Excellence through Education and Research) to rapidly collect descriptive data on patients with tinnitus and dizziness visiting participating CHEER sites. Study Design. Prospective observational data collection study over 6 months. Setting. Twenty one community otology and otolaryngology practices in the United States. Subjects and Methods. As proof of concept, a data collection study was developed for patients with tinnitus and dizziness (presenting with or without associated migraine) through a collaborative effort of the CHEER principal investigator (PI) and co-PIs. The 9-page questionnaire included validated instruments and additional patient- and physician-reported information. Information was captured electronically via REDCap by each site’s CHEER research coordinator. Site initiation, data entry rates, and research coordinator feedback were also collected. Results. Of the 21 CHEER sites, 15 participated in the study. Nine sites entered a patient within the first 31 days of study initiation, and all 15 sites were entering patients and corresponding clinical data within 72 days. During the 6-month study, 1044 patients were entered into the REDCap database. Research coordinator engagement was a major driver for success, whereas time and resources were deterrents. Incentives included altruism, professional development, and future financial opportunities. Conclusion. The CHEER research network has significant capability and infrastructure to collect prospective data in a practice-based environment. Research coordinator engagement undergirds network success; however, future efforts will cultivate stronger collaboration of the coordinator and site PI. Central coordination of practice-based research through a hub and spoke concept can be successful.

Is tinnitus an acoasm?
Med Hypotheses. 2011 May 5. [Epub ahead of print]

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Tinnitus and unspecific auditory hallucinations generally known as acoasms arise from identical or at least similar cerebral structures. Both phenomena can be interpreted as signs of an over activation of neuronal networks. Several pieces of evidence to underline this hypothesis as well as its implications are discussed. It is even speculated that both clinical entities might profit from treatment strategies that are normally employed for treatment of the other. Copyright © 2011 Elsevier Ltd. All rights reserved.
Tinnitus: patients do not have to 'just live with it'.

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Tinnitus is distressing and affects the quality of life for many patients. Because primary care physicians may be the entry point for patients seeking help for tinnitus, we urge them to acknowledge this symptom and its potential negative impact on the patient’s health and quality of life. Physicians should actively listen to the patient and provide hope and encouragement, but also provide realistic expectations about the course of treatment. The patient must also understand that there may be no singular „cure“ for tinnitus and that management may involve multidisciplinary assessment and treatment. Comment on Cleve Clin J Med. 2011 May;78(5):320.

XIV Case Reports

Apheresis as rescue therapy in a severe case of sudden hearing loss.

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A 23-year-old man complained of progressive left ear hearing loss and tinnitus and was unsuccessfully treated with steroids and mannitol. Four months later he presented with sudden, severe, asymmetrical, bilateral sensorineural hearing loss. The results of the laboratory workup were normal except for antinuclear autoantibodies. Auditory brain stem responses showed absent peak and interpeak latencies on both sides. The combination of plasma exchange with high doses of steroids resulted in a definite improvement. Plasmapheresis combined with steroid administration can be used as second-line therapy in idiopathic, sudden sensorineural hearing loss.

An unusual dark pigmentation on the tympanic membrane.

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Objective: To report an extremely rare case of dark pigmentation on the tympanic membrane due to alkaptonuria, and to discuss the probable association between this condition and hearing loss. Case report: A 58-year-old man with alkaptonuria was admitted with tinnitus and hearing loss in both ears. Physical examination showed bluish-black pigmentation on the helixes of both ears and both sclerae. Otoscopic examination revealed dark discoulouration of both tympanic membranes. Audiological evaluation revealed mixed high frequency hearing loss in both ears. Tympanometric examination revealed type A tympanograms bilaterally, and absence of acoustic reflexes both ipsilaterally and contralaterally. Computed tomography of the temporal bones revealed no abnormality. Conclusion: Clinicians should consider alkaptonuria in the differential diagnosis of patients with abnormal tympanic membrane pigmentation and hearing loss.
Carotid artery dissection, one of the most common causes of stroke in patients younger than 40 years of age, may develop spontaneously or after trauma. In 85% of cases, central neurological signs such as stroke, transient ischemic attack and amarozis fugax are seen, while headache and cranial nerve paralysis can be the presenting symptoms in the rest of cases. In this case report, a 35-year of age young male patient who had a progressive carotid artery dissection accompanied by complaints of left sided tinnitus and ipsilateral head and neck pain. The patient was admitted to the clinic with the diagnosis of carotid artery dissection and cerebral angiography (CA) was planned. During the CA performed the day after, three stents were placed in the dissection area. Improvement was observed in all complaints of the patient who was followed up in the clinic for 10 days. The patient was discharged in a healthy condition to return after three months for a control.

Ultrasound Characteristics of a Glomus Jugulare Tumor.
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A 33-year-old woman presented a chronic headache and sore throat on the right side of her body, continuous pulsatile tinnitus with decreasing hearing in the right ear, and recurrent bleeding from the right ear. Computer tomography and magnetic resonance imaging scan depicted a mass in the external ear canal and an enlarged right jugular bulb, which was revealed on duplex ultrasound in the upper portion of the right internal jugular vein. Surgical dissection of the tumor was performed. Pathological study revealed the mass was glomus jugulare tumor.

A case of multiple dural arteriovenous fistulas treated by multiple modalities.
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The authors report a rare case of multiple intracranial dural arteriovenous fistulas (DAVF) at separate sinuses. A 70-year-old man was introduced to our hospital complaining of visual disturbance due to bilateral choked disk, headache, and tinnitus. Initial angiography showed DAVFs involving the superior sagittal sinus and bilateral transverse-sigmoid sinuses, and the occlusion of the right jugular vein. The patient developed progressive impairment of visual activity and had high intracranial pressure (ICP) caused by venous hypertension. No cerebral alteration was seen on magnetic resonance imaging. To decrease the high ICP, surgical sinus isolation of the superior sagittal sinus was performed. After the surgery, transvenous embolization was performed to the right transverse-sigmoid sinus DAVF. Headache and tinnitus improved after these treatments, but visual activities rapidly declined and he experienced blindness in just a few months. Gamma knife radiosurgery was performed to the residual DAVFs. We discussed the etiology and treatment of the multiple DAVF, and reviewed past literatures.
Tinnitus as an unusual presentation of Schneiderian papillomatosis.

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INTRODUCTION: Primary Schneiderian papillomatosis of the middle ear and mastoid cavity is extremely rare. It is frequently associated with intermittent unilateral otorrhoea and mass in the middle ear and mastoid cavity. METHODS: Case presentation, symptoms, diagnostic criteria, management and literature review are discussed. CONCLUSION: Schneiderian papillomatosis is an important differential diagnosis of mass in the middle ear and mastoid cavity, and tinnitus as a presenting symptom has not been reported before. Primary radical treatment is essential in preventing tumour recurrence.

Short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA) secondary to epidermoid cyst in the right cerebellopontine angle successfully treated with surgery.

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Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) syndrome is a rare headache syndrome classified among the trigeminal autonomic cephalalgias. It is usually idiopathic, although infrequent secondary forms have been described. Recently, the term short-lasting unilateral headache with cranial autonomic symptoms (SUNA) has been defined by the International Headache Society (ICHD-2) as similar to SUNCT with less prominent absent conjunctival injection and lacrimation. We report a patient with paroxysmal orbito-temporal pains, phenotypically suggesting SUNA, secondary to epidermoid cyst in the cerebellopontine angle which disappeared after tumor resection. Neuroimaging should be considered in all patients with SUNA, notably in those with atypical presentation as our patient who presented on examination trigeminal hypoesthesia and tinnitus. Realization of a brain MRI would rule out injuries that causes this type of syndrome.

[Efficacy of first-line radiation for non-resectable carotid paraganglioma.]
[Article in French]


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BACKGROUND: Carotid paragangliomas are rare. Surgical resection is the primary treatment. However, when surgery is impossible, radiation therapy is an alternative potentially enabling local control with less morbidity. We report a case of good local control of an unresectable paraganglioma after external beam radiation. CASE REPORT: A 72-year-old-woman, had a 4-year history of right facial palsy associated with pulsatile tinnitus, episodic ear bleeding and ipsilateral hearing loss. Physical examination revealed a retro-mandibular and sub-mastoid pulsatile mass. Magnetic resonance imaging showed a large carotid paraganglioma involving the temporal bone. Since surgical resection was impossible, our patient was given external beam radiation therapy at a dose of 60 Gy. At 12 months follow-up, local control was good without significant toxicity. CONCLUSION: External beam radiation therapy seems to be a good alternative therapy for local control of carotid paragangliomas if surgical resection is impossible.
Persistence of multiple emissary veins of posterior fossa with unusual origin of left petrosquamosal sinus from mastoid emissary.

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Emissary veins are valveless veins which pass through the cranial apertures and connect the dural venous sinuses and the extracranial veins. The clinical importance of emissary veins is increasingly being appreciated. Some emissary veins like the petrosquamosal sinus and mastoid emissary vein may cause significant bleeding during middle ear and skull base surgeries. A dilated mastoid emissary vein or condylar emissary vein can sometimes be a rare cause of tinnitus. Radiological identification of these venous channels has been described in recent years and assumes significance in light of their clinical importance. We describe the CT and MRI findings of a rare case that had persistence of multiple emissary veins and presented clinically with tinnitus. The radiological findings included a dilated left mastoid emissary vein, bilateral petrosquamosal sinuses, posterior condylar veins, occipital emissary veins and an intrapetrous venule. The left petrosquamosal sinus had an unusual origin from the dilated mastoid emissary vein. The patient also had major anomalies of posterior fossa venous sinuses which are discussed. A relevant review of literature is included.

Cavernous hemangioma of the tympanic membrane.

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Cavernous hemangioma seems to most frequently arise in the posterior portion of the external auditory canal. However, they rarely occur in the tympanic membrane. A 49-year-old male patient was referred for evaluation of right-sided pulsatile tinnitus that he’d experienced for the previous 2 years. Temporal bone computerized tomography showed an isolated soft tissue mass just lateral to the tympanic membrane. There was no evidence of bony erosion or middle ear invasion. The patient underwent excision of the mass using a postauricular approach. The mass was removed en bloc and the defect of the tympanic membrane was repaired by tympanoplasty type I. There was no recurrence after 1 year of follow-up.

[Article in German]
HNO. 2011 May 5. [Epub ahead of print]

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We present the case of a female patient suffering from recurrent vertigo and low-frequency hearing loss who was admitted for inpatient treatment with the diagnosis of Ménière’s disease. After evaluation of all diagnostic examinations, including psychosomatic evaluation, a diagnosis of vestibular migraine with accompanying psychogenic vertigo could be confirmed and was treated accordingly. Neurotologic findings and the corresponding literature are reported.
Complete Endovascular Occlusion of a Cranial Dural Fistula using a Venous „To the Point“ Approach.
Cen Eur Neurosurg. 2011 May 2. [Epub ahead of print]

Gizewski ER, Göricke SL, Ozkan N, Grams AE, Ladd ME, Sure U, Forsting M.

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BACKGROUND AND OBJECT: Cranial dural arteriovenous fistulas are commonly treated using an endovascular method. In comparison to intracerebral arteriovenous malformations, it is important to reach the venous part of these malformations to maintain a complete occlusion. Therefore, often the venous side is totally occluded using coils and/or glue.

PATIENT AND METHODS: We describe a patient with an initially Type IIab (Cognard classification) left occipital cranial fistula. The patient suffered from an intense pulsate tinnitus. Therefore, the first embolization was performed using an approach via the dilated left middle meningeal artery using Onyx. The shunt of the fistula was reduced significantly but total occlusion was impossible. Therefore, the venous approach was used. Over a guiding catheter in the sigmoid sinus, the venous side of the fistula could be reached with a microcatheter. This part of the fistula was then completely occluded using coated and bare coils, without occluding the adjacent sinus. Control angiography of all previous feeders showed a complete occlusion of the fistula (used classification: Cognard ).

RESULTS: The fistula was entirely occluded. The patient’s outcome was excellent. The patient did not develop any symptoms and no complication occurred due to the treatment.

CONCLUSIONS: Direct occlusion of the venous part of an arteriovenous cranial fistula can be an option before an occlusion of the sinus has to be performed. This approach can lead to reduction of risk during the endovascular procedure and risk reduction in long-term follow-up. © Georg Thieme Verlag KG Stuttgart • New York.

Pulsatile tinnitus as a first symptom of essential thrombocythemia.

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Tinnitus is the sensation of sound inside the head and is a common symptom encountered daily by otorhinolaryngologists. Pulsatile tinnitus sufferers hear rhythmical noise at the same rate as a heartbeat and can present a diagnostic challenge. In this report, we present a 32-year-old patient with pulsatile tinnitus that led to the diagnosis of essential thrombocythemia. The symptom of pulsatile tinnitus allowed an early diagnosis of essential thrombocythemia and a more favorable prognosis. The case demonstrates the importance of blood tests for all patients who present with pulsatile tinnitus of unknown origin. Copyright © 2011 Elsevier Inc. All rights reserved.

A dural arteriovenous fistula in cavernous sinus developed from viral meningitis.


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Although hormonal influences, inflammation, trauma, sinus thrombosis, venous hypertension, and congenital origin have been proposed as sources of dural arterio venous fistulas (DAVFs) in cavernous and sigmoid sinuses, the etiology of these lesions remains controversial. We present a case with a cavernous sinus DAVF developed from viral meningitis which has not been previously described. A 24-year-old male was admitted to our institute because of periorbital pain, decreased vision, pulsatile tinnitus, chemosis, and exophthalmos on the right side after he had suffered viral meningitis four months
before. Cerebral angiography demonstrated a cavernous sinus DAVF, which was successfully obliterated with several platinum coils using a transvenous approach. The viral meningitis most likely caused the inflammation, that may be responsible for the occurrence of the cavernous sinus DAVF. Prompt treatment for inflammation may help to prevent the development of DAVFs. © Copyright 2011 Elsevier B.V., All rights reserved.

XV Specific Forms of Tinnitus


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Introduction. Although tinnitus often has a significant impact on individual's life, there are still few reports relating to tinnitus in children. In our tinnitus clinic, children with distressing tinnitus constitute about 0.5% of all our patients. Objectives. The aim of this study was to analyse children with troublesome tinnitus as regards epidemiology, audiological profile, and preliminary effects of the therapy. Methods. A retrospective study was carried out involving the cases of 143 children consulted in our Tinnitus Clinic in 2009. The selected group with troublesome tinnitus was evaluated and classified for proper category of Tinnitus Retraining Therapy (TRT). Results. The study showed that 41.3% of the children suffered from bothersome tinnitus. In this group 44.1% of the patients demonstrated normal hearing. The success of the therapy after 6 months was estimated on 81.4% of significant improvement. Conclusions. It is recommended that a questionnaire include an inquiry about the presence of tinnitus during hearing screening tests.

Intracochlear Schwannomas Confined to the Otic Capsule.

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OBJECTIVE: To determine the natural history and management for patients with intracochlear schwannomas.

STUDY DESIGN: Retrospective case series of intracochlear schwannomas confined to the otic capsule.

SETTING: Tertiary referral center.

PATIENTS: Ten patients were found to have schwannomas limited to the cochlea from 1998 to 2009.

INTERVENTIONS: All subjects underwent at least 1 magnetic resonance imaging (MRI) study and had at least 1 audiogram. Two patients underwent a transotic excision for intractable symptoms.

MAIN OUTCOME MEASURES: Presenting symptoms, initial and follow-up MRI findings, audiometric testing results, and need for surgical intervention were recorded for each subject.

RESULTS: Hearing loss was present in all 10 patients at their initial presentation. Tinnitus was present in 50% of patients, and vertigo was present in 30% of patients. No patient presented with aural fullness or facial weakness. The pattern of hearing loss seemed to correlate with the location of the lesion within the cochlea. Of the 9 patients that had follow-up MRIs, 3 patients showed tumor growth. Two of the 10 patients underwent surgical excision for intractable vertigo that resulted in resolution of symptoms.

CONCLUSION: Hearing loss is the most common finding in patients with intracochlear schwannomas, followed by tinnitus and vertigo. If the patient does not have symptoms of intractable vertigo, observation with serial MRI scans is indicated. Surgical excision should be reserved for patients with intractable vertigo or with significant tumor growth.
Carotid artery dissection: three cases and a review of the literature.

Schelfaut D, Dhondt E, De Raedt S, Nieboer K, Hubloue I.

Departments of aEmergency Medicine b Neurology c Radiology, Universitair Ziekenhuis Brussel, Brussels, Belgium.

Carotid artery dissections are potentially disabling, probably underdiagnosed, and mainly affect young-aged and middle-aged people. We present three consecutive cases illustrating different clinical presentations and thereby emphasizing the diagnostic challenge of carotid artery dissections for the emergency physician. Neck and facial pain, headache, unilateral pulsatile tinnitus, partial Horner’s syndrome (or oculosympathetic palsy), amaurosis fugax, retinal infarction, and anterior circulation brain ischemia may all occur in isolation or in various combinations. Medical imaging plays a pivotal role in making the right diagnosis. Clinical vigilance is of utmost importance as early diagnosis and timely treatment favor long-term prognosis and even prevent ischemic complications. We review the literature and discuss the pathophysiology, etiology, clinical presentation, diagnosis, imaging techniques, treatment, and prognosis of carotid dissections.

Associations between HLA-C Alleles and Definite Meniere’s Disease.


Otorhinolaryngology Research Center, Amir-Alam Hospital, Tehran University of Medical Sciences, Tehran, Iran. n_yazdani@sina.tums.ac.ir.

Both genetic and environmental factors seem to play role in the etiology of Meniere’s disease (MD). Several genes may be involved in susceptibility of MD including Human Leukocyte Antigens (HLA). The associations between MD and HLA alleles have been previously studied in other populations and certain HLA alleles were shown to be predisposing. The aim of this study was to determine the association between HLA-C allele frequencies and definite MD in patients who refer to Amir-Alam otolaryngology tertiary referral center in Tehran. Patients with definite MD (N=22) enrolled according to the diagnostic criteria of American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS). Cases with all 3 symptoms of MD (Vertigo, Tinnitus and lower frequency of sensory-neural hearing loss) were included and those with suspected MD were excluded from study. HLA-Cw allele frequencies were determined in patients non-related healthy controls (N=91) using PCR -SSP. We found that the frequency of HLACw*04 was significantly higher in patients compared to the controls [P = 0.0015, OR; 20, 95% CI (3.7-196.9)]. Our results revealed that HLA-C is a genetic predisposing factor in definite MD in patients who refer to Amir-Alam otolaryngology tertiary referral center.


Chang CC, Leslie DE, Spelman D, Chua K, Fairley CK, Street A, Crowe SM, Hoy JF.

Infectious Diseases Unit, The Alfred Hospital and Department of Medicine, Monash University, Vic. 3004, Australia.

Background The rise in serious complications of early syphilis, including neurosyphilis, particularly in those with HIV infection and in men who have sex with men (MSM), is of concern. Objectives: To review the manifestations and management of neurosyphilis in a population of HIV-infected MSM. Methods: Retrospective review of patients with HIV and early neurosyphilis in three centres in Melbourne, Australia, in 2000-07. Results: Eighteen male HIV patients met the criteria for diagnosis of early neurosyphilis. Thirteen patients (72.2%) had neurological symptoms: six with headache (33.3%),
four with tinnitus (22.2%) and five with impaired vision (27.8%), and one patient each with ataxia, leg weakness and anal discharge with faecal incontinence. Five patients (27.8%) reported no neurological symptoms. All had serum rapid plasma reagin (RPR) titres ≥1:32 and all except one had cerebrospinal fluid positive for syphilis fluorescent treponemal antibodies-absorbed. After treatment with 14-15 days of 1.8g intravenous benzylpenicillin 4-hourly, 12 of 17 patients (71%) demonstrated a four-fold drop in serum RPR titre over 6-12 months and were considered successfully treated. A rise in RPR was noted in three patients during the 12-month follow-up period, suggesting re-infection or recurrence. Conclusion: HIV-infected patients found to have syphilis either because of symptoms or by routine screening should be carefully assessed for neurological, ophthalmic and otological symptoms and signs. A low threshold for a diagnostic lumbar puncture to exclude the diagnosis of neurosyphilis enables appropriate administration and dose of penicillin for treatment, which appears successful in ~75% of cases.

Perilymphatic fistula of the round window.

Service ORL et centre d’implantation cochléaire, CHU Gui-de-Chauliac, 80, avenue Augustin-Fliche, 34295 Montpellier cedex 5, France.

To highlight diagnostic and treatment pitfalls in perilymphatic fistula.

Vertebral artery pexy for microvascular decompression of the facial nerve in the treatment of hemifacial spasm.

Ferreira M, Walcott BP, Nahed BV, Sekhar LN.
Department of Neurosurgery, University of Washington, Seattle, Washington; and.

Object Hemifacial spasm (HFS) is caused by arterial or venous compression of cranial nerve VII at its root exit zone. Traditionally, microvascular decompression of the facial nerve has been an effective treatment for posterior inferior and anterior inferior cerebellar artery as well as venous compression. The traditional technique involves Teflon felt or another construct to cushion the offending vessel from the facial nerve, or cautery and division of the offending vein. However, using this technique for severe vertebral artery (VA) compression can be ineffective and fraught with complications. The authors report the use of a new technique of VA pexy to the petrous or clival dura mater in patients with HFS attributed to a severely ectatic and tortuous VA, and detail the results in a series of patients. Methods Six patients with HFS due to VA compression underwent a retrosigmoid craniotomy, combined with a far-lateral approach in some patients. On identification of the site of VA compression, the vessel was mobilized adequately for the decompression. Great care was taken to avoid kinking the perforating vessels arising from the VA. Two 8-0 nylon sutures were passed through to the wall of the VA and then through the clival or petrous dura, and then tied to alleviate compression on cranial nerve VII. Results Patients were followed for at least 1 year postoperatively (mean 2.7 years, range 1-4 years). All 6 patients had complete resolution of their HFS. Facial function was tested postoperatively, and was stable when compared with the preoperative baseline. Two of the 3 patients with preoperative tinnitus had resolution of this symptom after the procedure. Postoperative imaging demonstrated VA decompression of the facial nerve and no evidence of stroke in all patients. One patient suffered from hearing loss, another developed a postoperative transient unilateral vocal cord paralysis, and a third patient developed a pseudomeningocele that resolved with the placement of a lumbar drain. Conclusions Hemifacial spasm and other neurovascular syndromes are effectively treated by repositioning the compressing artery. Careful study of the preoperative MR images may identify a select group of patients with HFS due to an ectatic VA. Rather than traditional decompression with only pledget placement, these patients may benefit from a VA pexy to provide an effective, safe, and durable resolution of their symptoms while minimizing surgical complications.
Long-term outcome in patients treated for benign dural arteriovenous fistulas of the posterior fossa.

Bink A, Berkefeld J, Kraus L, Senft C, Ziemann U, du Mesnil de Rochemont R.

Department of Neuroradiology, Johann Wolfgang Goethe University, Schleusenweg 2-16, Haus 95, 60528, Frankfurt am Main, Germany. andrea.bink@kgu.de.

INTRODUCTION: Dural arteriovenous fistula (dAVF) draining into a dural sinus without recruitment of cortical veins is regarded as relatively benign lesion and treatment is advocated only if the patient is severely affected by the symptoms. The aim of this study was to compare the clinical outcomes in patients who received endovascular treatment or no treatment, respectively.

METHODS: Twenty-one patients presented consecutively with pulsating tinnitus as leading symptom and with angiographically proven dAVF at the transverse or sigmoid sinus (Borden I). Nine patients underwent different types of endovascular embolisation, and 12 patients were not treated. After a median follow-up period of 2.3 years, outcome was evaluated by assessing the patients' symptoms and scores on the mRS, EQ-5D, SF-36 and HIT-6 scales.

RESULTS: Complete long-term closure of the dAFV was achieved in two out of nine cases; subtotal occlusion was found in seven patients. Pulsating tinnitus persisted less frequently in treated than in untreated patients. Neurologic symptoms occurred in both groups. Neither these findings nor the clinical outcome and scores on the quality-of-life scales varied substantially between the two groups.

CONCLUSION: Partial treatment did not resolve the clinical symptoms of patients with “benign” dural AVF in the follow-up and was not clearly superior to conservative management. These results suggest that embolisation should be offered only if there is a possibility of a complete cure without major periinterventional risks. Further studies should be performed to assess the risk-benefit ratio of pursuing more aggressive treatment strategies in patients with unbearable symptoms.

Intratympanic steroids for Ménière’s disease or syndrome.

Phillips JS, Westerberg B.

Department of Otolaryngology, Norfolk and Norwich University Hospital NHS Trust, Colney Lane, Norwich, UK, NR4 7UY.

BACKGROUND: Ménière’s disease is a disorder characterised by hearing loss, tinnitus and disabling vertigo. The use of intratympanic steroids to reduce the severity of these symptoms has been gaining popularity. OBJECTIVES: To assess the effectiveness of intratympanic steroids on the frequency and severity of attacks of vertigo, on chronic symptoms such as tinnitus, imbalance and hearing loss, and on the progression of these symptoms in patients with definite Ménière’s disease or syndrome, as defined by the AAO-HNS Committee. SEARCH STRATEGY: We searched the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL); PubMed; EMBASE; CINAHL; Web of Science; BIOSIS Previews; Cambridge Scientific Abstracts; ICTR and additional sources for published and unpublished trials. The date of the most recent search was 13 January 2011. SELECTION CRITERIA: Randomised controlled trials of intratympanic dexamethasone versus placebo in patients with Ménière’s disease. DATA COLLECTION AND ANALYSIS: Two authors independently assessed trial risk of bias and extracted data. We contacted study authors for further information where possible. MAIN RESULTS: A single trial containing 22 patients, with a low risk of bias was included. This trial found that after 24 months, compared with placebo, the use of intratympanic dexamethasone demonstrated a statistically significant improvement in vertigo as defined by a respective improvement in functional level (90% versus 42%), class (82% versus 57%), change in Dizziness Handicap Inventory scores (60.4 versus 41.3) and mean vertigo subjective improvement (90% versus 57%). The treatment regime described by the authors involved daily injections of dexamethasone solution 4 mg/ml for five consecutive days. These results were clinically significant. No complications were reported. AUTHORS’ CONCLUSIONS: The results of a single trial provide limited evidence...
to support the effectiveness of intratympanic steroids in patients with Ménière’s disease. This trial
demonstrated a statistically and clinically significant improvement of the frequency and severity of vertigo
measured 24 months after the treatment was administered. It is important to note that there were a few
aspects of the study which we were unable to clarify with the study authors.

Ear, Nose, and Throat Manifestations during Pregnancy.

Kumar R, Hayhurst KL, Robson AK.
Cumberland Infirmary, Carlisle, UK.

Objective. The objective of this clinical review is to highlight the otolaryngological symptoms that occur in
pregnancy. Where available, the authors discuss the current evidence of the etiology and management
of the various presentations. While it is appreciated that many of these complaints are transient, their
impact on the maternal quality of life can be significant, and therefore, medical practitioners should be
aware of what to expect in order to provide reassurance to patients and also to safely manage such
symptoms. Data Sources. MEDLINE and EMBASE databases were searched for publications related
to otolaryngology and pregnancy. Review Methods. All literature was searched for and reviewed
by 2 authors independently. Search results were then cross-examined, and any differences were
settled by consensus. Results. Pregnancy leads to circulatory changes and increased susceptibility to
viral reactivation, and along with the exertion of parturition, it can lead to tinnitus, facial palsies, and
deafness. Rising levels of sex hormones and heightened sensitivity to allergens may influence the nasal
mucosa, precipitating epistaxis and rhinitis. Increased progesterone and the increased intra-abdominal
pressure of the growing fetus can lead to symptoms and sequelae of laryngopharyngeal reflux.
Evidence for the treatment of pregnancy-induced symptoms is principally restricted to case reports and
retrospective studies. Conclusion. Recognition and understanding of pregnancy-related ear, nose, and
throat complaints will allow otolaryngologists to reassure and manage these patients, improving their
experience of the gestational period. High-quality evidence for their management is limited, with further
research required.
Clinical Trials

Source: clinicaltrials.gov (16th July 2011)

OTO-104 for the Treatment of Meniere's Disease

<table>
<thead>
<tr>
<th>Current status</th>
<th>not yet open for participant recruitment</th>
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</thead>
<tbody>
<tr>
<td>Sponsors and collaborators</td>
<td>Otonomy, Inc.</td>
</tr>
<tr>
<td>Information provided by</td>
<td>Otonomy, Inc.</td>
</tr>
<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT01412177</td>
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<tr>
<td>Purpose</td>
<td>The purpose of this study is to evaluate the effectiveness of OTO-104 for the treatment of Meniere's disease.</td>
</tr>
<tr>
<td>Condition(s)</td>
<td>Meniere's Disease</td>
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| Interventions | Drug: OTO-104  
Drug: Placebo |
| Phase | Phase II |
| Study type and design | Interventional  
Allocation: Randomized  
Endpoint Classification: Efficacy Study  
Intervention Model: Parallel Assignment  
Masking: Double Blind (Subject, Investigator, Outcomes Assessor)  
Primary Purpose: Treatment |
| Official title | A Prospective, Randomized, Double-blind, Placebo-controlled, Multicenter, Phase 2 Study of OTO-104 Given as a Single Intratympanic Injection in Subjects With Unilateral Meniere's Disease |
| Primary outcome measures | Reduction in vertigo frequency as measure of efficacy of OTO-104 in subjects with Meniere's disease [ Time Frame: 4 months ] [ Designated as safety issue: No ] |
| Secondary outcome measures | • Evaluation of adverse events, otoscopic exams, audiometry, Word Recognition Score and tympanometry as a measure of safety and tolerability [ Time Frame: 4 months ] [ Designated as safety issue: Yes]  
• Evaluation of tinnitus patient reported questionnaire and daily diary as a measure of impact of tinnitus on activities of daily living [ Time Frame: 4 months ] [ Designated as safety issue: No ]  
• Evaluation of patient reported questionnaires as a measure of impact on patient daily activities [ Time Frame: 4 months ] [ Designated as safety issue: No ] |
<p>| Estimated Enrollment | 140 |
| Study Start Date | September 2011 |
| Estimated Study Completion Date | August 2012 |</p>
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<tr>
<th>Estimated Primary Completion Date</th>
<th>June 2012 (Final data collection date for primary outcome measure)</th>
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<tr>
<td><strong>Arms</strong></td>
<td><strong>Assigned Interventions</strong></td>
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<tr>
<td>OTO-104 (steroid) 12 mg:</td>
<td>Drug: OTO-104</td>
</tr>
<tr>
<td>Experimental</td>
<td>Single intratympanic injection of 12 mg OTO-104.</td>
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<tr>
<td>Intervention: Drug: OTO-104</td>
<td></td>
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<tr>
<td>Vehicle for OTO-104: Placebo</td>
<td>Drug: Placebo</td>
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<tr>
<td>Comparator</td>
<td>Single intratympanic injection of placebo</td>
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<tr>
<td>Intervention: Drug: Placebo</td>
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<tr>
<td>Ages Eligible for Study</td>
<td>18 Years to 80 Years</td>
</tr>
<tr>
<td>Genders Eligible for Study</td>
<td>Both</td>
</tr>
<tr>
<td>Accepts Healthy Volunteers</td>
<td>No</td>
</tr>
<tr>
<td>Inclusion Criteria</td>
<td>• Subject has a diagnosis of unilateral Meniere’s disease by 1995 American Academy of Otolaryngology — Head and Neck Surgery (AAOHNSS) criteria and reports active vertigo for the 2 months prior to the study lead-in period.</td>
</tr>
<tr>
<td></td>
<td>• Subject has experienced active vertigo during the lead-in period.</td>
</tr>
<tr>
<td></td>
<td>• Subject has documented asymmetric sensorineural hearing loss.</td>
</tr>
<tr>
<td></td>
<td>• Subject agrees to maintain their current treatments for Meniere’s disease while on-study.</td>
</tr>
<tr>
<td></td>
<td>• Subjects currently on a low-salt diet and/or diuretic at the time of screening agree to continue this treatment throughout the study.</td>
</tr>
<tr>
<td>Exclusion Criteria</td>
<td>• Subject is pregnant or lactating.</td>
</tr>
<tr>
<td></td>
<td>• Subject has a history of immunodeficiency disease.</td>
</tr>
<tr>
<td></td>
<td>• Subject has a history of previous endolymphatic sac surgery.</td>
</tr>
<tr>
<td></td>
<td>• Subject has a history of previous use of intratympanic (IT) gentamicin in the affected ear.</td>
</tr>
<tr>
<td></td>
<td>• Subject has a history of tympanostomy tubes with evidence of perforation or lack of closure.</td>
</tr>
<tr>
<td></td>
<td>• Subject has experienced an adverse reaction to IT injection of steroids.</td>
</tr>
<tr>
<td></td>
<td>• Subject has used an investigational drug or device in the 3 months prior to screening.</td>
</tr>
<tr>
<td></td>
<td>• Subject has previously been randomized to a trial of OTO-104.</td>
</tr>
<tr>
<td>Contacts</td>
<td>Rebecca Calvert (423) 478-7474 <a href="mailto:RCalvert@INCResearch.com">RCalvert@INCResearch.com</a></td>
</tr>
<tr>
<td></td>
<td>Carl LeBel, PhD (858) 768-7819 <a href="mailto:CLeBel@Otonomy.com">CLeBel@Otonomy.com</a></td>
</tr>
<tr>
<td>Responsible Party</td>
<td>Otonomy, Inc. (Carl LeBel, PhD, Chief Scientific Officer)</td>
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<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT01412177</td>
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<td>Other Study ID Numbers</td>
<td>104-201102</td>
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<tr>
<td>Study First Received</td>
<td>July 31, 2011</td>
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Cognitive Speed as an Objective Measure of Tinnitus (COMeT)

Current status | currently recruiting participants
Sponsors and collaborators | Washington University School of Medicine
Information provided by | Washington University School of Medicine
ClinicalTrials.gov Identifier | NCT01395368

Purpose
Tinnitus, commonly referred to as “ringing in the ears”, affects 50 million people in the United States and is recognized as a major public health concern. Tinnitus is the most frequent cause of service-connected disability claims among war veterans. Tinnitus remains a subjectively diagnosed entity. There is no standardized objective method of diagnosing tinnitus or describing the functional impact of the condition. Currently, physicians have to rely on patient-based self reports. Without an objective method of diagnosing tinnitus and describing the functional implications, adequate treatment delivery is also hampered since there is no way to objectively stratify patients into severity groups and assess response to treatment. Because tinnitus is known to negatively affect cognition through the ventral attention networks and the prefrontal cortex, measuring cognitive processing speed is a possible way to objectively measure tinnitus. This study builds on previous work the investigators have done that utilized a quick, easily accessible measure of auditory processing speed. That earlier study showed a correlation between that measure and self reported measures of tinnitus severity, and this study attempts determine a more precise estimate of that correlation. It also better validates those results by including a traditional neurocognitive measuring cognitive speed and by controlling for the presence of depression and somatoform disorders.

Condition(s) | Tinnitus
Interventions | Behavioral: Brain Speed Test
Study type and design | Observational
| Observational Model: Case-Only
| Time Perspective: Cross-Sectional
Official title | Cognitive Speed as an Objective Measure of Tinnitus
Estimated Enrollment | 150
Study start | June 2011
<table>
<thead>
<tr>
<th>Groups / Cohorts</th>
<th>Tinnitus</th>
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<tbody>
<tr>
<td>Participants must be between the ages of 18 and 80. Participants must have subjective, unilateral or bilateral, non-pulsatile tinnitus of 6 month’s duration or longer.</td>
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| Intervention: Behavioral: Brain Speed Test |

<table>
<thead>
<tr>
<th>Assigned Interventions</th>
<th>Behavioral: Brain Speed Test</th>
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</thead>
<tbody>
<tr>
<td>Performance on Brain Speed Test</td>
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<table>
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<tr>
<th>Participants (age)</th>
<th>18 Years to 80 Years</th>
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<table>
<thead>
<tr>
<th>Gender</th>
<th>Both</th>
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<table>
<thead>
<tr>
<th>Accepts healthy volunteers</th>
<th>No</th>
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</table>

<table>
<thead>
<tr>
<th>Sampling Method</th>
<th>Non-Probability Sample</th>
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<table>
<thead>
<tr>
<th>Study population</th>
<th>The study population will include men and women between the ages of 18-80 years who have subjective, unilateral or bilateral, non-pulsatile tinnitus of 6 month’s duration or longer.</th>
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</thead>
</table>

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>• Participants must be between the ages of 18 and 80.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Participants must have subjective, unilateral or bilateral, non-pulsatile tinnitus of 6 month’s duration or longer.</td>
</tr>
<tr>
<td></td>
<td>• Participants must be able to read, write and speak using the English language.</td>
</tr>
<tr>
<td></td>
<td>• Participants must be able to read and follow the instructions for both computerized tests, “The Brain Speed Test” and “The 60 Second Brain Game.”</td>
</tr>
<tr>
<td></td>
<td>• Participants must be able to provide written informed consent.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion Criteria</th>
<th>• Participants with tinnitus related to Workman’s Compensation Claim or other litigation-related situations.</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>• Participants with active diagnoses of any acute or chronic brain-related neurological conditions that alter normal brain anatomy or function including Parkinson’s disease, Multiple Sclerosis, Alzheimer’s Disease, cerebral infarcts, traumatic brain injury, history of brain tumor(s), epilepsy, or dementia.</td>
</tr>
<tr>
<td></td>
<td>• Participants with tinnitus related to retrocochlear lesions, cochlear implants, or other known anatomic/structural lesions of the brain, skull-base, temporal bone or ear.</td>
</tr>
<tr>
<td></td>
<td>• Participants who have a hearing threshold above 90 dB on any of the tested frequencies during audiometry.</td>
</tr>
<tr>
<td></td>
<td>• Participants unable to hear the highest volume of the computer-based objective assessments.</td>
</tr>
<tr>
<td></td>
<td>• Participants taking any medications that may affect or alter cognition including but not limited to sedatives, hypnotics, narcotics, or opiates.</td>
</tr>
<tr>
<td></td>
<td>• Participants with any medical condition the PI determines would compromise the safety of the participant or complicate the interpretation of the study results.</td>
</tr>
</tbody>
</table>
### Contact
Neil Das, BS
636.362.9475
DasS@ent.wustl.edu

### Locations
United States, Missouri
Washington University Recruiting
St. Louis, Missouri, United States, 63110

### Responsible Party
Washington University School of Medicine (Phyllis Klein, RN, CCRC, BSN)

### ClinicalTrials.gov Identifier
NCT01395368

### Study ID Numbers
201103191

### Last Updated
July 14, 2011

### Record first received
July 13, 2011

### Health Authority
United States: Institutional Review Board

## Exploration of Cortical Neural Network in Patients With Bothersome Tinnitus

<table>
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<tr>
<th>Current status</th>
<th>currently recruiting participants</th>
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<tr>
<td>Sponsors and collaborators</td>
<td>Washington University School of Medicine</td>
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<td>Information provided by</td>
<td>Washington University School of Medicine</td>
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<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT01385540</td>
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<tr>
<td>Purpose</td>
<td>This will be an experimental task-based functional MRI pilot study involving the neuroimaging assessment of patients with severely bothersome tinnitus, defined by a global bothersome scale. The investigators plan to enroll a total of 12 participants (6 severely bothered tinnitus and 6 age-matched non-tinnitus controls) over the course of six months to undergo task-based imaging. Subjects in the tinnitus group may have previously participated in the CTRWU study (HRPO: 07-0689) conducted by Dr. Jay Piccirillo at Washington University and have given permission to be contacted for consideration in future studies. The selected paradigm will allow us to advance knowledge about the role of the attention, control, and other cortical networks in the development and maintenance of bothersome tinnitus.</td>
</tr>
<tr>
<td>Condition(s)</td>
<td>Tinnitus</td>
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<tr>
<td>Interventions</td>
<td>Behavioral: Task-Based Functional Magnetic Resonance Imaging (fMRI)</td>
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<tr>
<td>Study type and design</td>
<td>Observational</td>
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<tr>
<td>Official title</td>
<td>Exploration of Cortical Neural Network in Patients With Bothersome Tinnitus</td>
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</tbody>
</table>
**Detailed Description**

Task-Based Functional Magnetic Resonance Imaging (fMRI) The task-based fMRI protocol is based on work performed at Washington University by Dr. Gordon Shulman and published in The Journal of Neuroscience. (Shulman, Astafiev, Franke, Pope, Snyder, McAvoy, and Corbetta 2009) Individuals will be shown a target, which is randomly selected from 12 objects designated as targets, before each scan. The target for a scan will never appear as a non-target object in another scan. Per established protocol, individuals will fixate on a central cross prior to imaging. Individuals will press a MR-compatible button when they detect the target. Target objects only appear in the cued stream. Cues, a filled red square, are programmed to occur, on average, every 2.06, 4.12, or 6.18 seconds within a temporal window of ± 400 milliseconds centered on those values.

<table>
<thead>
<tr>
<th>Estimated Enrollment</th>
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<tbody>
<tr>
<td>Study start</td>
<td>July 2011</td>
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<tr>
<td>Expected study completion date</td>
<td>November 2011</td>
</tr>
<tr>
<td>Expected primary completion date</td>
<td>August 2011 (Final data collection date for primary outcome measure)</td>
</tr>
<tr>
<td>Groups / Cohorts</td>
<td>Task-based fMRI Intervention: Behavioral: Task-Based Functional Magnetic Resonance Imaging (fMRI)</td>
</tr>
<tr>
<td>Assigned Intervention</td>
<td>Behavioral: Task-Based Functional Magnetic Resonance Imaging (fMRI) Individuals will be shown a target, which is randomly selected from 12 objects designated as targets, before each scan. The target for a scan will never appear as a non-target object in another scan. Per established protocol, individuals will fixate on a central cross prior to imaging. Individuals will press a MR-compatible button when they detect the target. Target objects only appear in the cued stream. Cues, a filled red square, are programmed to occur, on average, every 2.06, 4.12, or 6.18 seconds within a temporal window of ± 400 milliseconds centered on those values.</td>
</tr>
<tr>
<td>Participants (age)</td>
<td>18 Years to 60 Years</td>
</tr>
<tr>
<td>Gender</td>
<td>Both</td>
</tr>
<tr>
<td>Accepts health volunteers</td>
<td>Yes</td>
</tr>
<tr>
<td>Sampling Method</td>
<td>Non-Probability Sample</td>
</tr>
<tr>
<td>Study Population</td>
<td>Target population will consist of 12 adult participants - 6 with moderately, severely or worse, bothersome tinnitus, based on both a global bothersome score (i.e. How bothered are you by your tinnitus?) and the Tinnitus Handicap Index (THI). THI is a 25-question survey designed to assess how much tinnitus affects a person-possible scores range from 0-100, with a score 38 falling in the 75th percentile. The other six participants (Control group) will be age-matched without tinnitus.</td>
</tr>
</tbody>
</table>
| Inclusion Criteria | • Men and women between the ages of 18 to 60  
  • Subjective, unilateral or bilateral, non-pulsatile tinnitus of 6 month’s duration or greater  
  • Either “moderately bothered” or “severely bothered” on the Global Bothersome scale  
  • THI score of ≥ 30.  
  • Able to give written informed consent  
  • Able to read, write, speak and understand English fluently |
| Exclusion Criteria | • Tinnitus related to cochlear implantation, retrocochlear lesion, or other known anatomic lesions of the ear and temporal bone  
  • History of Ménière’s Disease  
  • History of hyperacusis or misophonia (hyper-sensitivity to noises)  
  • Cardiac pacemakers, intracardiac lines, implanted medication pumps, implanted electrodes in the brain, or any other contraindication for MRI scan  
  • An acute or chronic unstable medical condition which, in the opinion of the investigator, would require stabilization prior to testing.  
  • Any active ear disease that, in the opinion of the PI or mentor, needs to be further evaluated  
  • A Short Blessed Test score of 9 or greater  
  • PHQ-9 score ≥ 10; consistent with diagnosis of moderate depression.  
  • History of seizure disorder or other neurological condition.  
  • Any psychiatric co-morbidity that may complicate the interpretation of study results. Subjects may not be currently taking antidepressants.  
  • Any tinnitus related to a Workman’s Compensation claim or litigation-related event  
  • Currently pregnant: Women of childbearing potential must have a negative urine pregnancy test prior to MRI  
  • Weight over 300 pounds  
  • History of claustrophobia  
  • Inability to lay flat for 2 hours  
  • Active alcohol and/or drug dependence or history of alcohol and/or drug dependence within the last year  
  • Any medical condition that, in the opinion of the investigators, confounds study results or places the subject at greater risk  
  • Unable to provide written informed consent  
  • Blindness or inability to see screen for task-based testing without eyeglasses, subjects may wear contacts if able to lie flat and keep eyes focused on testing screen for up to 2 hours.  
  • Previous participation in a task-based MRI study |
| Contact | Andre Wineland, MD, Washington University School of Medicine, phone 314.362.5296, winelanda@ent.wustl.edu |
A Study on the Effect of Cilostazol in Patients With Chronic Tinnitus (CITI-ESR)

Current status
not yet open for participant recruitment

Sponsors and collaborators
Asan Medical Center
Korea Otsuka Pharmaceutical Co., Ltd.

Information provided by
Asan Medical Center

ClinicalTrials.gov Identifier
NCT01378650

Purpose
1. Overview of tinnitus
Tinnitus is a noisy sound which is perceived without any external sound source. According to the survey of the US, 10-20% of adults have the symptom of tinnitus and 3-5% of tinnitus patients have severe discomfort of daily life. Severe tinnitus can result in psychiatric problems such as depression and anxiety disorders. Enhancement of environmental sound, hearing aids, sound generators, cognitive therapy, transcranial magnetic therapy, and drug therapy have been tried for treatment of tinnitus. Nitric oxide (NO) is a well-known neurotransmitter acting as a vasodilator through regulation of production of cyclic guanosine monophosphate (cGMP) and can be found in various sites of cochlea. It is reported that cGMP enhances activity of protein kinase A (PKA), a mediator of platelet aggregation inhibition and vasodilatation and results in increase of vascular flow.

2. Characteristics of the clinical research drug, cilostazol
Cilostazol inhibits phosphodiesterase type 3 (PDE3) selectively and increases amount of cAMP by inhibition of degradation of cyclic adenosine monophosphate (cAMP). cAMP again by increasing the active form of PKA suppress the production of blood clots and increase blood flow by expanding blood vessels. Anti-platelet activity and vasodilation effect of cilostazol have been used for improvement of diabetic peripheral vascular disorders and suppression of stroke recurrence. Previous studies reported that by increasing the activity of NO and PKA, the blood flow of stria vascularis and cochlear hair cells can be improved. These studies imply that cilostazol, which causes inhibition of PDE3 and increase of PKA, can have a potential effect on improvement of tinnitus by increase of blood flow to peripheral cochlear cells. Thus,
we hypothesized that cilostazol, which has been widely used for enhancing peripheral blood flow, can bring improvement of tinnitus by causing better peripheral blood flow of cochlea.

3. The aim of the study We planned this study to validate the assumptions of the background. The aim of our study is whether administration of cilostazol can improve tinnitus in terms of subjective degree of symptoms in chronic tinnitus patients.

<table>
<thead>
<tr>
<th>Condition(s)</th>
<th>Tinnitus</th>
</tr>
</thead>
</table>
| Interventions | Drug: Cilostazol  
Drug: Placebo |
| Study type and design | Interventional  
Allocation: Randomized  
Endpoint Classification: Efficacy Study  
Intervention Model: Parallel Assignment  
Masking: Double Blind (Subject, Caregiver, Investigator)  
Primary Purpose: Treatment |
| Official title: | A Randomized, Prospective, Placebo-controlled Double-blind, Pilot Study on the Effect of Cilostazol for 4 Weeks in Patients With Chronic Tinnitus |
| Detailed description | 1. Clinical research methods  
• Determination of eligibility by history taking, physical examination, pure tone audiometry, speech audiometry, and distortion product otoacoustic emission test.  
• Randomization by random sequence generation  
• Administration: cilostazol 100mg Bid 4 weeks for the study group and placebo tablet Bid 4 weeks for the control group.  
• Evaluation battery: questionnaires (tinnitus handicap inventory, visual analogue scale, Quality of life SF-36)  
• Time of evaluation: pre-administration, 2 weeks after administration, 4 week after administration  
• Monitoring of side effects  
2. Evaluation of treatment response - Statistical analysis of scores of questionnaires using SPSS K12.0 (paired t-test for changes of each group and Mann-Whitney U test for comparing the mean scores of two groups) |
| Primary outcomes | Primary Outcome Measures  
• Change of the tinnitus handicap inventory (THI) score [ Time Frame: pre-administration, 2 weeks after administration, 4 week after administration ] [ Designated as safety issue: No ]  
• A Questionnaire for assessing subjective discomfort from chronic tinnitus  
• Change of the visual analogue scale (VAS) score [ Time Frame: pre-administration, 2 weeks after administration, 4 week after administration ] [ Designated as safety issue: No ]  
• A Questionnaire for assessing subjective discomfort from chronic tinnitus |
<table>
<thead>
<tr>
<th>Change of Quality of life (SF-36) score</th>
<th>Time Frame: pre-administration, 2 weeks after administration, 4 week after administration</th>
<th>Designated as safety issue: No</th>
</tr>
</thead>
<tbody>
<tr>
<td>A questionnaire for assessing subjective discomfort from chronic tinnitus</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Expected total Enrollment** 50

**Study start** July 2011

**Expected study completion date** December 2011

**Expected primary completion date** December 2011 (Final data collection date for primary outcome measure)

<table>
<thead>
<tr>
<th><strong>Arms</strong></th>
<th><strong>Assigned Interventions</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cilostazol group: Experimental</strong></td>
<td><strong>Drug</strong>: Cilostazol</td>
</tr>
<tr>
<td><strong>Administration of Cilostazol 100mg twice a day for 4 weeks</strong></td>
<td><strong>Intervention</strong>: Drug: Cilostazol</td>
</tr>
<tr>
<td><strong>Placebo group: Placebo Comparator</strong></td>
<td><strong>Drug</strong>: Placebo placebo one tablelet matching for cilostazol twice a day for 4 weeks.</td>
</tr>
<tr>
<td><strong>Intervention: Drug</strong>: Placebo</td>
<td></td>
</tr>
</tbody>
</table>

**Participants (age)** 20 Years and older

**Gender** both

**Accepts healthy volunteers** no

**Inclusion Criteria**
- Adults of age over 19
- Unilateral or bilateral tinnitus
- Chronic tinnitus lasting more than 3 months
- Initial visual analogue scale of tinnitus >3

**Exclusion Criteria**
- Conductive hearing loss on pure tone audiometry
- Associated other inner ear diseases such as Meniere’s disease
- Objective or pulsatile tinnitus
- Contraindication to anti-platelet drug
- Any cardiac disease
- Bleeding tendency and major operation within 3 months
- Breastfeeding
- Pregnancy

**Contact** Jong Woo Chung, M.D. +82-2-3010-3718 ext 3718 gfinder.jw@gmail.com

**Locations** Korea, Republic of Asan Medical Center Seoul, Korea, Republic of, 138-736
<table>
<thead>
<tr>
<th>Responsible Party</th>
<th>Asan Medical Center (Jong Woo Chung, M.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study chairs or principal investigators</td>
<td>Jong Woo Chung, M.D. Asan Medical Center</td>
</tr>
<tr>
<td>Study ID Numbers</td>
<td>AMC-2010-0800, KCT0000128</td>
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<tr>
<td>Last Updated</td>
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<td>June 21, 2011</td>
</tr>
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<td>ClinicalTrials.gov Identifier</td>
<td>NCT01378650</td>
</tr>
<tr>
<td>Health Authority</td>
<td>South Korea: Korea Food and Drug Administration (KFDA)</td>
</tr>
</tbody>
</table>