Dear Colleagues,

Thank you very much for the feedback to the First TRI Newsletter. We tried to realize your advices and we would be very pleased to act on every of your further suggestion!

Within the second TRI Newsletter you find an additional section compared to the First TRI Newsletter: The section Clinical Trials contains an overview about registered trials that are underway and is intended to appear regularly. In the future we will limit the information to newly registered trials.

Concerning the literature section the question came up why some categories are listed even if there are no publications therein. To allow easier orientation among the newly published literature we present the categories in a fixed order. Therefore some categories may remain empty in a certain newsletter.

Last but not least we want to inform you that the TRI website www.tinnitusresearch.org has been renewed. Especially we want to draw your attention to the new sections “Collecting Ideas” and “Easy Grants”.

Susanne Staudinger
Berthold Langguth
News

Grant program of the American Hearing Research Foundation
The American Hearing Research Foundation is calling for research proposals in the area of hearing and balance disorders related to the inner ear of their 2008 funding cycle.
For more information and application procedures see www.american-hearing.org.

Grant program of the American Tinnitus Association
The American Tinnitus Association offers awards of up to $300,000 over three years for proposals directly related to tinnitus. Deadline for application is Saturday, 30 June 2007.
For more information about the grants see http://www.ata.org/research/research_faq.html
An application form you will find at http://www.ata.org/research/apply.html
Contact amy@ata.org or by phone 800-634-8978 x218
Upcoming Meetings

May 2007

Annual Electric Response Audiometry and Oto-Acoustic Emissions (ERA & OAE) Course
When: May, 14 – 18, 2007
Where: Harrogate, UK
Contact: Dr Guy Lightfoot
E-Mail: g.lightfoot@liverpool.ac.uk

June 2007

The International Evoked Response Audiometry Study Group (IERASG)
XXth biennial symposium
When: June, 10 – 14, 2007
Where: Bled, Slovenia
Contact: Dr. Dušan Butinar
Phone: ++386-1-522-1514
Fax: ++386-1-522-1533
E-Mail: dusan.butinar@kclj.si

VII Süddeutsches Tinnitus-Symposium
“10 Jahre Klinik Am Stiftsberg” / 20 Jahre DTL, Bad Grönenbach
When: June, 22 -23 2007
Where: Klinik “Am Stiftsberg”, Bad Grönenbach
Contact: Frau Andrea Tafler
Phone: +49 83 34 98 15 02
Detailed information: http://www.tinnitus-liga.de/termine.htm

Advances in Tinnitus – Assessment, Treatment & Neuroscience Basis
When: June 22 – 24, 2007
Where: Holiday Inn Grand Island Resort and Conference Center
Grand Island, New York, USA
Register online at http://wings.buffalo.edu/faculty/research/chd
Or get a registration form by e-mail caltman@buffalo.edu
or by phone +1-716-829-2001
Detailed information: http://wings.buffalo.edu/faculty/research/chd

12. Bad Meinberger Tinnitus-Symposium der Deutschen Tinnitus-Liga
Grenzen erkennen - Ressourcen ausschöpfen
When: June 29 – 30, 2007
Where: Kurgastzentrum Horn-Bad Meinberg
Contact: Frau von Dombrowski
E-Mail: g.dombrowski@tinnitus-liga.de
Phone: +49 202-24 65 212
Fax: +49 202-24 65 220,
Detailed information: http://www.tinnitus-liga.de/termine.htm
6th MOLECULAR BIOLOGY OF HEARING AND DEAFNESS CONFERENCE  
When: July 11-14, 2007  
Where: Wellcome Trust Conference Centre, Sanger Institute at Hinxton, UK  
Detailed information: [http://www.wellcome.ac.uk/node6233.html](http://www.wellcome.ac.uk/node6233.html)

2nd Tinnitus Research Initiative Meeting  
Together for a cure of Tinnitus – challenging our basic assumptions  
When: July 17 – 21, 2007  
Where: Principality of Monaco  
Contact: Tinnitus Research Initiative  
Phone: +49-941-941-2096  
E-Mail: info@tinnitusresearch.org  
Detailed information: [www.tinnitusresearch.org](http://www.tinnitusresearch.org)

Biology of the Inner Ear: Experimental and analytical approaches  
When: August 19 - September 1, 2007  
Detailed information: [www.mbl.edu/education/courses/special_topics/bie.html](http://www.mbl.edu/education/courses/special_topics/bie.html)

2007 Annual Meeting & OTO EXPO  
When: September 16 – 29, 2007  
Where: Washington D.C., USA  
Contact: American Academy of Otolaryngology – Head and Neck Surgery  
Phone: +1-703-836-4444  
Fax: +1-703-683-5100  
E-Mail: OTOEXPO@entnet.org  
or [meetings@entnet.org](mailto:meetings@entnet.org)  
Detailed information: [http://www.entlink.net/meetings/meetings/Annual-Prep.cfm](http://www.entlink.net/meetings/meetings/Annual-Prep.cfm)

Fifteenth annual Conference on Management of the tinnitus patient  
When: September 20 – 22, 2007  
Where: University of Iowa, Iowa City  
Contact: Richard Tyler PhD  
Phone: +1-319-356-2471  
E-Mail: rich-tyler@uiowa.edu  

British Tinnitus Association – BTA Conference 2007  
Tinnitus – The Way Ahead  
When: Thursday 4 October 2007  
Where: The Royal College of Surgeons, London, UK  
Detailed information: [http://www.tinnitus.org.uk/events/conf07/conf07.htm](http://www.tinnitus.org.uk/events/conf07/conf07.htm)
October 2007

Aging and Speech Communication: An international and interdisciplinary research conference
When: October 7-10, 2007
Where: Indiana University, Bloomington
Detailed information: http://www.indiana.edu/~ascpost/index.htm

November

Neuroscience 2007, the Society's 37th annual meeting
When: November 3-7, 2007
Where: San Diego, California
Detailed information: http://www.sfn.org/am2007/?CFID=7679509&CFTOKEN=57216251

June 2008

IXth International Tinnitus Seminars
When: June 15 – 18, 2008
Where: Göteborg, Sweden
Contact: Congrex Sweden AB, Ref. Tinnitus 2008
P.O.Box 5078
402 22 Göteborg, Sweden
Phone: +46-31-708-6000
Fax: +46-31-708-6025
E-Mail: tinnitus2008@congrex.com
Detailed information: http://www.congrex.se/ITS2008

July 2008

The 10th International Workshop on the Mechanism of Hearing
When: July 27 – 31, 2008
Where: Keele University, UK
Contact: Dr. N.P. Cooper
School of Life Sciences
Keele University
Keele, Staffordshire
ST5 5BG
UK
Phone: +44-1782-583056
Fax: +44-1782-583055
E-Mail: secretary@mechanicsofhearing.com
Detailed information: http://www.mechanicsofhearing.com
I Epidemiology

[Rock music and hearing disorders]
[Article in Norwegian]

Stormer CC Stenklev NC
Institutt for klinisk medisin, Det medisinske fakultet, Universitetet i Tromso, 9037 Tromso. carl.christian.lein.stormer@gmail.com

Background: Continued exposition to loud noise is a well-known risk factor for development of various hearing disorders; rock musicians are especially vulnerable. The aim of this paper was to get an overview of hearing loss, tinnitus and hyperacusis among rock musicians.

Material and method: Medline was systematically searched, using combinations of the terms „hearing“, „rock music“, „tinnitus“ and „hyperacusis“.

Results and interpretation: Seven publications concerning hearing of rock musicians were identified. Permanent hearing loss occurred in 20% (mean) of the rock musicians; the prevalence varied from 5 to 41%. Tinnitus and hyperacusis appear significantly more often in rock musicians than in non-musicians. Rock musicians have increased resistance against loud music and exposure over time is protective towards hearing loss. Further research is needed to assess rock music’s impact on musicians’ hearing.

II Pathophysiology

Objective tinnitus due to essential palatal tremor in a 5-year-old.

Macdonald JT
Department of Pediatrics, Division of Pediatric Clinical Neuroscience, University of Minnesota, Minneapolis, Minnesota.

A healthy 5-year-old male reported a clicking sound in both ears. Neurologic examination was normal except for an audible clicking noise that could be heard when within 10 cm of either ear and bilateral rapid rhythmic movements of the soft palate. All tests were normal including magnetic resonance imaging brain scan. One year after onset, his objective tinnitus and palatal tremor were no longer present.

Otosyphilis: a review of 85 cases.

Yimtae K, Srirompotong S, Lertsukprasert K
Department of Otolaryngology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand. kwayim@kku.ac.th

Objective: To review the clinical manifestations and the follow-up hearing results of the treatment modalities in the patients with otosyphilis.

Study design and setting: A retrospective review between 1984 and 2000 at a university hospital. Patients who presented with cochleovestibular symptoms and were confirmed seropositive for specific treponemal tests were included. Excluded were patients older than 70, or who had other identified causes of cochleovestibular symptoms.
**Results:** Subjects included 56 males and 29 females with an average age of 59.5 years (range, 40 to 70). Common presenting symptoms included hearing loss (90.6%), tinnitus (72.9%), and vertigo (52.9%). The cerebrospinal fluid analysis was positive in 5.4%. The overall respective hearing results in the short- and long-term follow-up were improved or stable in 93.4% and 83.3% of patients. Even though adding steroids and neurosyphilis regimens tended to improve and stabilize hearing, the results were not statistically significant among treatment modalities.

**Conclusion:** Further study about hearing outcomes among treatment modalities is suggested.

**Neuropathic and cerebrovascular correlates of hearing loss in Fabry disease.**


**Ries M, Kim HJ, Zalewski CK, Mastroianni MA, Moore DF, Brady RO, Dambrosia JM, Schiffmann R, Brewer CC**

Developmental and Metabolic Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD 20892-1260, USA.

Fabry disease, OMIM 301500, is a progressive multisystem storage disorder due to the deficiency of alpha-galactosidase A (GALA). Neurological and vascular manifestations of this disorder with regard to hearing loss have not been analysed quantitatively in large cohorts. We conducted a retrospective cross sectional analysis of hearing loss in 109 male and female patients with Fabry disease who were referred to and seen at the Clinical Center of the National Institutes of Health, Bethesda, MD, USA on natural history and enzyme replacement study protocols. There were 85 males aged 6-58 years (mean 31 years, SD 13) and 24 females aged 22-72 years (mean 42 years, SD 12). All patients underwent a comprehensive audiological evaluation. In addition, cerebral white matter lesions, peripheral neuropathy, and kidney function were quantitatively assessed. HL(95), defined as a hearing threshold above the 95th percentile for age and gender matched normal controls, was present in 56% [95% CI (42.2-67.2)] of the males. Prevalence of HL(95) was lower in the group of patients with residual GALA enzyme activity compared with those without detectable activity (33% versus 63%) HL(95) was present in the low-, mid- and high-frequency ranges for all ages. Male patients with HL(95) had a higher microvascular cerebral white matter lesion load [1.4, interquartile range (IQR) 0-30.1 +/- versus 0, IQR 0-0], more pronounced cold perception deficit [19.4 +/- 5.5 versus 13.5 +/- 5.5 of just noticeable difference (JND) units] and lower kidney function [creatinine: 1.6 +/- 1.2 versus 0.77 +/- 0.2 mg/dl; blood urea nitrogen (BUN): 20.1 +/- 14.1 versus 10.3 +/- 3.28 mg/dl] than those without HL(95) (P < 0.001). Of the females, 38% had HL(95). There was no significant association with cold perception deficit, creatinine or BUN in the females. Word recognition and acoustic reflexes analyses suggested a predominant cochlear involvement. We conclude that hearing loss involving all frequency regions significantly contributes to morbidity in patients with Fabry disease. Our quantitative analysis suggests a correlation of neuropathic and vascular damage with hearing loss in the males. Residual GALA activity appears to have a protective effect against hearing loss.

[Hearing loss in patients with Fabry disease.]

[Article in German]


**Limberger A, Beck M, Delgado-Sanchez S, Keilmann A**

Klinik fur HNO und Kommunikationsstörungen, Universitätsklinik Mainz, Langenbeckstrasse 1, 55101, Mainz, Deutschland, limberger@kommunikation.klinik.uni-mainz.de.

**Background:** Fabry disease is an X-linked lysosomal storage disease involving deficient activity of alpha-galactosidase A, which leads initially to pain, and later to renal insufficiency, cardiomyopathy and stroke. Until now few details are available on hearing impairment in patients with Fabry disease, and especially few relating to female patients.

**Patients and methods:** We examined 43 female and 29 male patients. In this study we looked into the question of whether and to what extent patients of both genders are affected by hearing impairment.
**Results:** Hearing loss is characteristic being more severe at high frequencies. Overall, 22 female and 15 male patients were found to have suffered a hearing loss. Patients with severe symptoms of Fabry disease usually demonstrate more prominent hearing losses.

**Conclusions:** Both men and women with Fabry disease are affected by hearing impairment. It seems that the hearing loss is less marked in female than in male patients. Children with Fabry disease complain of *tinnitus* more frequently than other children and quite early in the course of the disease.

**Intense sound-induced plasticity in the dorsal cochlear nucleus of rats: Evidence for cholinergic receptor upregulation.**


Kaltenbach JA, Zhang J

Department of Otolaryngology-Head and Neck Surgery, Wayne State University, School of Medicine, Detroit, MI 48201, United States.

Previous studies in a number of species have demonstrated that spontaneous activity in the dorsal cochlear nucleus (DCN) becomes elevated following exposure to intense sound. This condition of hyperactivity has aroused considerable interest because it may represent an important neural correlate of *tinnitus*. There is some evidence that neurons in the superficial DCN, such as cartwheel, stellate and fusiform cells, may contribute to the level of hyperactivity induced by intense sound, although the relative importance of these different cell types is unknown. In the present study, we sought to determine the effect of intense sound exposure on multiunit spontaneous activity both at the DCN surface and in the fusiform cell layer and to examine the influence of cholinergic input to DCN circuits on the level of activity in the fusiform cell layer. Rats were studied in two groups, one of which had been exposed to a continuous intense sound (10kHz 127dB SPL) for 4h while the other group served as unexposed controls. Between 30 and 52 days post-exposure, recordings of multiunit activity were performed at the DCN surface as well as in the middle of the fusiform cell layer. Changes in fusiform cell layer activity were also studied in response to superficial applications of the cholinergic agonist, carbachol, either alone or following pre-application of the cholinergic antagonist, atropine. The results demonstrated that multiunit spontaneous activity in the rat DCN was generally much higher in both control and exposed animals relative to that which has been observed in other species. This activity was significantly higher at the DCN surface of sound-exposed animals than that of controls. In contrast, hyperactivity could not be demonstrated in the fusiform cell layer of sound-exposed animals. Carbachol administration most commonly caused suppression of fusiform cell layer activity. However, this suppression was considerably stronger in the DCN of sound-exposed animals than in controls. These findings suggest that hyperactivity at the DCN surface of exposed rats may arise as a consequence of more highly activated neurons in the molecular layer, such as cartwheel and/or stellate cells, and that the lack of hyperactivity in the fusiform cell layer may be the result of inhibition of fusiform cells by these inhibitory interneurons. Although this finding does not rule out fusiform cells as possible sources of hyperactivity in other species, or even in the rat after short post-exposure recovery periods, the enhanced sensitivity of the fusiform cell layer to cholinergic stimulation suggests that in the rat, at least after prolonged post-exposure recovery periods, increased inhibition of activity in this layer by more superficially located neurons may result from an upregulation of receptors for cholinergic input. This upregulation may be greater in rats than in other species due to the relatively heavy cholinergic input that exists in the cochlear nucleus of this species.
Salicylate induced tinnitus: Behavioral measures and neural activity in auditory cortex of awake rats.


Center for Hearing and Deafness, Department of Communicative Disorders and Sciences, University at Buffalo, Buffalo, NY 14214, United States; Department of Otolaryngology, YueYang Hospital, Shanghai, China.

Neurophysiological studies of salicylate-induced tinnitus have generally been carried out under anesthesia, a condition that abolishes the perception of tinnitus and depresses neural activity. To overcome these limitations, measurement of salicylate induced tinnitus were obtained from rats using schedule induced polydipsia avoidance conditioning (SIPAC) and gap pre-pulse inhibition of acoustic startle (GPIAS). Both behavioral measures indicated that tinnitus was present after treatment with 150 and 250mg/kg of salicylate; measurements with GPIAS indicated that the pitch of the tinnitus was near 16kHz. Chronically implanted microwire electrode arrays were used to monitor the local field potentials and spontaneous discharge rate from multiunit clusters in the auditory cortex of awake rats before and after treatment with 150mg/kg of salicylate. The amplitude of the local field potential elicited with 60dB SPL tone bursts increased significantly 2h after salicylate treatment particularly at 16-20kHz; frequencies associated with the tinnitus pitch. Field potential amplitudes had largely recovered 1-2 days post-salicylate when behavioral results showed that tinnitus was absent. The mean spontaneous spike recorded from the same multiunit cluster pre- and post-salicylate decreased from 22spikes/s before treatment to 14spikes/s 2h post-salicylate and recovered 1 day post-treatment. These preliminary physiology data suggest that salicylate induced tinnitus is associated with sound evoked hyperactivity in auditory cortex and spontaneous hypoactivity.

Psychological characteristics of patients with Meniere's disease compared with patients with vertigo, tinnitus, or hearing loss.

Ear Nose Throat J. 2007 Mar;86(3):148-156

Savastano M, Marioni G, Aita M
ENT Section, Department of Medical-Surgical Specialities, Padova University Hospital, Padova, Italy.
marina.savastano@unipd.it

An association between Meniere's disease and psychological distress is frequently reported. Patients who do not have Meniere's disease but who have similar symptoms also experience various kinds of psychological disturbances. We conducted a study to investigate the relationship between Meniere's disease and personality traits, illness behavior, depression, and anxiety. We compared these factors in 77 patients who had Meniere's disease and 133 controls who did not have the disease but had one of its symptoms--either vertigo, tinnitus, or hearing loss. The mental status of study participants was assessed with standard tests. Patients in both groups had higher than normal levels of anxiety and neuroticism. The only significant difference between the two groups was a higher rate of extroversion in the Meniere's disease group. Minor differences emerged when Meniere's patients with tinnitus or vertigo were compared with similar controls. Relationships between psychological observations and otologic symptomatology or an otologic diagnosis were not specific, which illustrates the need to consider the role of illness behavior and personality as targets for psychological support or therapy associated with ENT treatment.
V Pharmacotherapy

[Botulinum toxin treatment in the head and neck region: Current aspects, developments, and problems.]
[Article in German]
HNO. 2007 Mar 14; [Epub ahead of print]

Laskawi R
Universitats-HNO-Klinik, Robert-Koch-Strasse 40, 37075, Gottingen, Deutschland, rlaskaw@gwdg.de.

Some interesting developments, aspects, and problems concerning botulinum toxin treatment of disorders of the head and neck region have recently been reported. These new approaches are discussed in this review. They include applications into mimic muscles (prevention of scar formation, treatment of depressions), into laryngeal muscles, and into the upper esophagus. In addition, treatment of different forms of headache and tinnitus as well as applications in the autonomic nervous system are addressed. Some of these options will shortly be put into clinical use, while others have to be checked further in clinical studies.

Special issue of Hearing Research:
Pharmacological strategies for prevention and treatment of hearing loss and tinnitus.

Editorial

Barbara Canlon1, Guest Editors, Donald Henderson and Richard Salvi2
1Karolinska Institutet, Sweden, 2State University of New York at Buffalo, USA

The goal of this special issue is to focus on major developments related to the biological mechanisms that underlie noise, drug and age-related hearing loss and tinnitus and to review some of the new pharmacologic approaches to prevention and treatments of hearing loss and tinnitus. Hearing loss and tinnitus have long been recognized as serious and pervasive health problems. In industrialized societies where noise levels are increasing, hearing loss in the young and middle aged builds up over many years as a result of incessant exposure to moderate levels of noise in the work place (e.g., machinery) or recreational environments (e.g., loud music, motor cycles). In some cases, the onset of hearing loss and tinnitus occur almost immediately after extremely high level impact (e.g., jack hammer) or impulse noise (e.g., gun fire, explosion). Nowhere is the problem more serious than in the military where approximately 30% of combat personnel develop significant hearing loss or tinnitus. The Veterans Administration ranks hearing loss and tinnitus among its 10 most common disabilities.

Drugs used to treat life threatening infections or malignant tumors may prolong an individual's life, but at the expense of developing severe high frequency hearing loss and tinnitus. Cisplatin, which is widely used to treat many forms of cancer leads to irreversible high-frequency hearing loss in approximately 30% of children and in adults the incidence of hearing loss ranges from 4% to 91%. Aminoglycoside antibiotics, which are extremely effective in treating gram negative bacterial infections are seldom used in the West because they are both ototoxic and nephrotoxic. However, aminoglycoside antibiotics are among the most widely used antibiotics in third world countries because of their low cost and therapeutic efficacy.

Those who manage to avoid hearing loss in early life cannot escape the ravages of age. By age 65, approximately 31% of the population has significant age-related hearing loss or presbycusis. By age 75, the prevalence increases to nearly 50%. Hearing loss is often accompanied by tinnitus, the ringing, rushing, buzzing or clicking sensation that occurs in the absence of sound. Approximately, 12 million American seek medical treatment for tinnitus; and of these, 2 million experience tinnitus that is severe and disabling. For more than 50 years, the prevention and treatment of hearing loss and tinnitus has largely focused on prevention, avoiding ototoxic drugs and high level noise that cause hearing loss or wearing
hearing protectors. However, during the past decade scientists in many disciplines, including those working on the inner ear, have made enormous progress in understanding the biochemical events that can trigger the death of hair cells and spiral ganglion neurons either by necrosis or the carefully orchestrated, biochemical cell death process known as apoptosis. A common theme that has emerged from recent studies of hearing loss from noise, ototoxic drugs or aging is that hearing loss is initiated by oxidative stress involving the overproduction of reactive oxygen species that overwhelm the cell’s antioxidant defense system. In order to dissect out the role of cellular antioxidant enzymes in noise, drug or age-related hearing loss, researchers have used gene therapy approaches or transgenic or knockout mice that over or under express antioxidant enzymes or genes that enhance or inhibit apoptosis. Others have used pharmacologic strategies to upregulate antioxidant defenses or to block specific cell death pathways.

While the signaling pathways that modulate or regulate cell death from noise exposure, ototoxic drugs and aging are likely to share some similarities there may be important differences. Pharmacologic compounds that protect against aminoglycoside ototoxicity may or may not protect against cisplatin, acoustic trauma or aging. The biological pathways that lead to noise, drug or age-related hearing loss may vary with the degree of stress imposed by a particular agent. Compounds that protect against low levels of stress may be ineffective at higher levels of stress. Animal studies have illustrated the important role that genetic factors have on age-related hearing loss as well as noise and drug-induced hearing loss. Knowledge of the role specific genes play in hearing loss may one day lead to individualized pharmacological treatments for preventing hearing loss. Armed with the knowledge that oxidative stress is an important factor in noise, age and drug induced hearing loss, auditory scientists and clinicians have tested a host of compounds designed to scavenge or inactivate ROS, boost or upregulate cellular antioxidant defense systems or block apoptotic pathways. Animals studies of noise, drug or age-related hearing loss that have shown promise in the laboratory are gradually making their way into translational research studies aimed at evaluating the clinical efficacy of different therapeutic approaches.

Tinnitus is a continuously growing problem in all societies and often occurs together with hearing loss. Tinnitus is also accompanied by hyperacusis, and sometimes depression, indicating altered processing of both auditory information and non-auditory information, as well as altered expression of neural plasticity. At present, there is no general treatment for tinnitus, but there are several treatments that can alleviate or reduce the symptoms in some patients. Antidepressant drugs have been successfully used to treat tinnitus in some patients with and without depressive symptoms. The basis for this therapy is based on the interplay between non-auditory brainstem structures and the central auditory pathways. Attempts to develop effective tinnitus therapies will benefit from a greater understanding of how the activity in the auditory pathway is altered by different states of activation of these non-auditory brainstem structures and vice versa. Pharmacological strategies for tinnitus have been hampered by the lack of suitable animal models. Salicylate-induced tinnitus is one of the animal models used over many years and is yielding information on the mechanisms responsible for this disorder. Reviewed in this Special Issue is a combination of new theoretical and experimental approaches, together with clinical findings that are increasing our understanding of tinnitus, its origin, underlying causes and its suppression.

The organizers, with cooperation from the National Institute for Occupational Safety and Health, believed that research on cochlear therapeutics had advanced to the state that it would be interesting and useful to arrange a meeting of leading scientists and representatives from the pharmaceutical industry. The US Army, with guidance provided by Col. Nancy Vause, recognized the importance of the meeting very early in the planning stages and arranged financial support for the invited speakers and guidance for future development. The meeting was held in Niagara Falls, Ontario in October, 2005. In this special issue of Hearing Research are key papers that were presented at the meeting. The intellectual design was to review the states of conventional protection strategies and then move into pharmacological prevention of noise-induced hearing loss, presbycusis drug induced hearing loss and tinnitus.
Antidepressant therapy in tinnitus.


Robinson SK, Viirre ES, Stein MB
Department of Psychiatry, University of California, San Diego School of Medicine, Veterans Administration San Diego Healthcare System, 3350 La Jolla Village Dr., Mail Code 116A, La Jolla, CA 92161, USA.

Objective: Review the literature on the co-morbidity of depression and anxiety with tinnitus. Briefly consider proposed mechanisms by which antidepressants might be helpful for tinnitus, including treatment of co-morbid depression and anxiety and a more direct serotonergic mechanism of tinnitus. Survey the literature on antidepressants and tinnitus including tinnitus reported as a side effect of antidepressants (phenelzine, amitriptyline, protriptyline, doxepin, imipramine, fluoxetine, trazadone, bupropion, venlafaxine), tinnitus associated with withdrawal of antidepressants (venlafaxine and sertraline) and antidepressants as a treatment for tinnitus (case reports - fluoxetine and paroxetine, retrospective reviews - imipramine and selective serotonin reuptake inhibitors, single blind trials of amitriptyline and double blind placebo controlled trials of trimipramine, nortriptyline, paroxetine and sertraline). Provide suggestions on future directions, specifically replication of prior studies and a dose finding study of paroxetine for the treatment of tinnitus.

Intense sound-induced plasticity in the dorsal cochlear nucleus of rats: Evidence for cholinergic receptor upregulation.


Kaltenbach JA, Zhang J
Department of Otolaryngology-Head and Neck Surgery, Wayne State University, School of Medicine, Detroit, MI 48201, United States.

Previous studies in a number of species have demonstrated that spontaneous activity in the dorsal cochlear nucleus (DCN) becomes elevated following exposure to intense sound. This condition of hyperactivity has aroused considerable interest because it may represent an important neural correlate of tinnitus. There is some evidence that neurons in the superficial DCN, such as cartwheel, stellate and fusiform cells, may contribute to the level of hyperactivity induced by intense sound, although the relative importance of these different cell types is unknown. In the present study, we sought to determine the effect of intense sound exposure on multiunit spontaneous activity both at the DCN surface and in the fusiform cell layer and to examine the influence of cholinergic input to DCN circuits on the level of activity in the fusiform cell layer. Rats were studied in two groups, one of which had been exposed to a continuous intense sound (10kHz 127dB SPL) for 4h while the other group served as unexposed controls. Between 30 and 52 days post-exposure, recordings of multiunit activity were performed at the DCN surface as well as in the middle of the fusiform cell layer. Changes in fusiform cell layer activity were also studied in response to superficial applications of the cholinergic agonist, carbachol, either alone or following pre-application of the cholinergic antagonist, atropine. The results demonstrated that multiunit spontaneous activity in the rat DCN was generally much higher in both control and exposed animals relative to that which has been observed in other species. This activity was significantly higher at the DCN surface of sound-exposed animals than that of controls. In contrast, hyperactivity could not be demonstrated in the fusiform cell layer of sound-exposed animals. Carbachol administration most commonly caused suppression of fusiform cell layer activity. However, this suppression was considerably stronger in the DCN of sound-exposed animals than in controls. These findings suggest that, hyperactivity at the DCN surface of exposed rats may arise as a consequence of more highly activated neurons in the molecular layer, such as cartwheel and/or stellate cells, and that the lack of hyperactivity in the fusiform cell layer may be the result of inhibition of fusiform cells by these inhibitory interneurons. Although this finding does not rule out fusiform cells as possible sources of hyperactivity in other species, or even in the rat after short post-exposure recovery periods, the enhanced sensitivity of the fusiform cell layer to cholinergic stimulation...
suggests that in the rat, at least after prolonged post-exposure recovery periods, increased inhibition of activity in this layer by more superficially located neurons may result from an upregulation of receptors for cholinergic input. This upregulation may be greater in rats than in other species due to the relatively heavy cholinergic input that exists in the cochlear nucleus of this species.

Antioxidant therapy in idiopathic tinnitus: preliminary outcomes.
Savastano M, Brescia G, Marioni G
Department of Otolaryngology Head Neck Surgery, Padua University, Padua, Italy.

Background: Reactive oxygen species (ROS) play an important role in several pathogenic processes, damaging various structural and functional cellular components. The endothelium is at major risk of radical-induced lesions and this damage is most manifest in microcirculation. It has been recently observed that ROS are implicated in the pathology of the inner ear and the peripheral and central pathways. In a previous study we detected high serum values of ROS in subjects with idiopathic tinnitus. The purpose of the present study was to evaluate the validity of antioxidant treatment in tinnitus sufferers with high ROS values.

Methods: The study considered 31 consecutive patients with unilateral idiopathic tinnitus. The mean pure tone audiometric threshold (PTA), tinnitus loudness, subjective disturbance level [visual analogue scale (VAS) determination], and the indirect ROS dosage 48 h before and after medical treatment were evaluated. Patients underwent an 18-week oral treatment with a mix of phospholipids and vitamins (glycerophosphorylcholine, glycerophosphorylethanolamine, beta-carotene, vitamin C, vitamin E).

Results: ROS levels were significantly reduced following antioxidant treatment (malonaldehyde: 2.10 vs. 1.98 mumol/dL, p = 0.003; 4-hydroxynonenal: 2.36 vs. 2.16 mumol/dL, p = 0.002) In addition, great improvement was observed in the reduction of tinnitus (VAS and tinnitus loudness evaluations). No significant changes in audiometric threshold occurred.

Conclusions: Oral antioxidant therapy in patients with idiopathic tinnitus seems to reduce the subjective discomfort and tinnitus intensity and may be considered as an additional treatment modality.

Westerlaken BO, de Kleine E, van der Laan B, Albers F
Department of Otohinolaryngology, University Medical Center Groningen, The Netherlands. b.o.westerlaken@kno.umcg.nl

Objectives: The etiology and treatment of idiopathic sudden sensorineural hearing loss (ISSHL) is still unclear. The anti-inflammatory effect of corticosteroids is thought to play an important part in the recovery from ISSHL. We aimed to determine whether a more powerful anti-inflammatory technique using pulse therapy is effective in the treatment of ISSHL.

Methods: In a randomized, prospective, double-blind, multicenter clinical trial, we recruited 81 patients with ISSHL. Patients were randomly allocated to pulse therapy (300 mg dexamethasone for 3 consecutive days followed by 4 days of placebo) or control treatment (prednisone 70 mg per day tapered in steps of 10 mg per day to 0 mg). The primary outcome was hearing recovery as measured by pure-tone audiometry and speech audiometry after 12 months. Secondary outcomes were subjective parameters such as hearing recovery, tinnitus, vertigo, and a pressure sensation in the ear.

Results: The overall improvement in pure-tone thresholds and speech discrimination scores was not significantly better in patients who were given dexamethasone than those who were given standard prednisone. Hearing improved from 71 dB HL to 36 dB HL in the dexamethasone group and from 75 dB HL to
42 dB HL in the prednisone group. Speech discrimination scores of 100% were achieved by 64% of dexamethasone-treated patients and by 57% of the prednisone group. Conclusion: Pulse therapy is equally effective and safe as standard-dose prednisone. Pulse therapy suppresses both humoral and cellular immune responses and therefore has a wider anti-inflammatory effect.

VI Auditive Stimulation
VII Brain Stimulation

Repetitive transcranial magnetic stimulation for tinnitus: a pilot study.
Laryngoscope. 2007 Mar;117(3):529-34.

Smith JA, Mennemeier M, Bartel T, Chelette KC, Kimbrell T, Triggs W, Dornhoffer JL
Department of Otolaryngology-Head and Neck Surgery, University of Arkansas for Medical Sciences, Little Rock, Arkansas 72205, USA.

Objectives/Hypotheses: Low-frequency repetitive transcranial magnetic stimulation (rTMS) has been shown to alleviate tinnitus perception, presumably by inhibiting cortical activity associated with tinnitus. We conducted a pilot study to assess effectiveness of neuronavigated rTMS and its effects on attentional deficits and cortical asymmetry in four patients with chronic tinnitus using objective and subjective measures and employing an optimization technique refined in our laboratory.

Study design: Randomized, placebo-controlled (sham stimulation) crossover study.

Methods: Patients received 5 consecutive days of active, low-frequency rTMS or sham treatment (using a 45-degree coil-tilt method) before crossing over. Subjective tinnitus was assessed at baseline, after each treatment, and 4 weeks later. Positron emission tomography/computed tomography (PET/CT) scans were obtained at baseline and immediately after active treatment to examine change in cortical asymmetry. Attentional vigilance was assessed at baseline and after each treatment using a simple reaction time test.

Results: All patients had a response to active (but not sham) rTMS, as indicated by their best tinnitus ratings; however, tinnitus returned in all patients by 4 weeks after active treatment. All patients had reduced cortical activity visualized on PET immediately after active rTMS. Mean reaction time improved (P < .05) after active but not sham rTMS.

Conclusions: rTMS is a promising treatment modality that can transiently diminish tinnitus in some individuals, but further trials are needed to determine the optimal techniques required to achieve a lasting response. It is unclear whether the improved reaction times were caused by tinnitus reduction or a general effect of rTMS. PET/CT scans immediately after treatment suggest that improvement may be related to reduction of cortical asymmetry associated with tinnitus.

VIII Behavioral Therapy
IX Somatic Tinnitus

[Botulinum toxin treatment in the head and neck region: Current aspects, developments, and problems.]
[Article in German]
HNO. 2007 Mar 14; [Epub ahead of print]

Laskawi R
Universitats-HNO-Klinik, Robert-Koch-Strasse 40, 37075, Gottingen, Deutschland, rlaskaw@gwdg.de.

Some interesting developments, aspects, and problems concerning botulinum toxin treatment of disorders of the head and neck region have recently been reported. These new approaches are discussed.
They include applications into mimic muscles (prevention of scar formation, treatment of depressions), into laryngeal muscles, and into the upper esophagus. In addition, treatment of different forms of headache and tinnitus as well as applications in the autonomic nervous system are addressed. Some of these options will shortly be put into clinical use, while others have to be checked further in clinical studies.

**X Surgical Treatment**

**Osteotome technique for removal of symptomatic ear canal exostoses.**

Hetzler DG  
Department of Otolaryngology-Head and Neck Surgery, Santa Cruz Medical Clinic, Inc., an affiliate of the Palo Alto Medical Foundation, Santa Cruz, California, USA. hetzled@sutterhealth.org

**Objectives/Hypothesis:** This study was undertaken to assess a transcanal osteotome technique for removing symptomatic ear canal exostoses. Outcome measures included healing rates and the rate of complications.

**Study design:** Prospective study in a private practice.

**Methods:** A straight 1-mm osteotome and a curved 1-mm osteotome were used by way of a transcanal approach to incrementally remove obstructive ear canal exostoses. If anterior or superior bone growths were closely approximating the tympanic membrane, they were partially removed with a 1.5 mm cylindrical end- and side-cutting burr. Healing rates were monitored with weekly postoperative visits.

**Results:** Two hundred twenty-one ear canals (140 patients) were consecutively treated with this technique. Healing was achieved at 2 to 8 (average 3.50) weeks, with 90% healed by 4 weeks. There were 4 mobilizations of a full-thickness segment of anterior bony canal wall; 3 exposures of periosteum anterior to the anterior bony wall; 1 tear of the tympanic membrane requiring a tympanoplasty; 18 anterior and 11 posterior tympanic membrane tears that healed spontaneously; 3 instances of new-onset postoperative tinnitus; and 1 instance of postoperative positioning vertigo. There were no lacerations of the tympanic membrane by an osteotome, no facial nerve injuries, no soft tissue stenoses of an ear canal, and no skin grafting of an ear canal.

**Conclusions:** The described technique of using osteotomes transcanal for removal of symptomatic obstructive ear canal exostoses promoted rapid healing and was effective and safe.

**XI Holistic**

**Neural correlates of transmeatal cochlear laser (TCL) stimulation in healthy human subjects.**

Department of Radiology II, Division of Neuroradiology, University Hospital of Innsbruck, Medical University Innsbruck, Anichstrasse 35, 6020 Innsbruck, Austria. christian.siedentopf@fmri-easy.de

Transmeatal cochlear laser (TCL) treatment has recently been proposed as a therapeutic procedure for cochlear dysfunction such as chronic cochlear tinnitus or sensorineural hearing loss. The aim of this study was to investigate whether TLC has any influence on the central nervous system using functional MRI with healthy young adults. The laser stimulation device was placed on the tympanic membrane of
both ears. A laser stimulation run and a placebo run were performed in random order. The participants were unable to differentiate between verum and placebo stimulation. In the comparison of verum to placebo runs, we observed significant activations within the left superior frontal gyrus, the right middle and medial frontal gyrus, the right superior parietal lobule, the left superior occipital gyrus, the precuneus and cuneus bilaterally, the right anterior and the left and right middle and posterior cingulate gyrus and the left thalamus. This network of brain areas corresponds well to results from previous PET studies of patients with tinnitus. Though TCL seems to have a clinically measurable effect on the central nervous system the neurophysiological mechanism leading to the observed activated neuronal network remains unknown.

XII Review

XIII Others

Survey of mobile phone use and their chronic effects on the hearing of a student population.
[Article in English, French]

Davidson HC, Lutman ME
Institute of Sound and Vibration Research, University of Southampton. Southampton. UK.

Mobile phone ownership and usage is now widespread and public concern has developed over possible harmful physiological effects of their use. This study aimed to investigate the prevalence of student mobile phone ownership and any possible chronic effects of usage on hearing, tinnitus and balance. Questionnaires for electronic self-completion were distributed to University of Southampton postgraduates, and 117 out of 160 returned met the criteria for analysis. A total of 94% were current mobile phone users, and only 2% had never used a mobile phone. Duration of ownership and daily usage ranged from 0-7 years and 0-45 minutes respectively. Text-messaging was more popular than talking. High or long-term users reported no worse hearing, tinnitus, or balance than low or short-term users. The results of this study confirm that the prevalence of mobile phone ownership amongst students is extremely high. However there appear to be no harmful effects of mobile phone usage on their audiovestibular systems within the range of exposure of the study, insofar as can be detected by the self-report method employed.

Impact of prognostic factors on recovery from sudden hearing loss.
J Laryngol Otol. 2007 Jan 23;;1-6 [Epub ahead of print]

Ceylan A, Celenk F, Kemaloglu YKBayazit YAGoksu N, Ozbi Dot Above Len S
Department of Otolaryngology, Gazi University School of Medicine, Ankara, Turkey.

Objective: To define the impact of patient-related and audiovestibular parameters on the prognosis of sudden hearing loss.

Methods: Eighty-three patients were included in this retrospective study. All were treated medically. We recorded the patients' demographic parameters, systemic diseases, time elapsed between onset of sudden hearing loss and initiation of treatment, tinnitus, vestibular symptoms, type of initial audiogram, pure tone averages and speech discrimination scores. For all patients, audiological measurements were performed on initial admission and at the completion of treatment on the 10th day.

Results: There was no correlation between the hearing gain and recovery rate scores and patients' gender or age (p>0.05). However, a correlation was found between gender and relative hearing gain. Vertigo was not correlated with hearing gain and recovery rate scores (p<0.05). However, relative hearing gain correlated negatively with the presence of vertigo (-r=0.05, 81 degrees of freedom, p=0.043). Patients with <40 dB hearing loss on admission showed a better relative hearing gain (r=0.55, 81 degrees of freedom, p=0.03).
Relative hearing gain correlated positively with better pre-treatment speech discrimination scores ($r=0.82$, $81$ degrees of freedom, $p=0.009$) and negatively with poorer pre-treatment pure tone averages ($-r=0.082$, $81$ degrees of freedom, $p=0.009$). There was no correlation between the scores for hearing gain, relative hearing gain and recovery rate and: systemic diseases ($p>0.05$); time elapsed between onset of sudden hearing loss and initiation of treatment ($p>0.05$); type of audiogram on initial admission ($p>0.05$), except for midfrequency type of audiogram; and tinnitus ($p>0.05$).

**Conclusions:** The outcome of sudden hearing loss was unaffected by systemic disease, tinnitus or type of audiogram (except for midfrequency type). The following were poor prognostic factors in the outcome of sudden hearing loss: female gender, presence of vertigo, initiation of treatment more than seven days after onset of hearing loss, and $>40$ dB hearing loss on admission.

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**Barotrauma and Decompression Illness of the Inner Ear: 46 Cases During Treatment and Follow-Up.**

Otol Neurotol. 2007 Apr 4; [Epub ahead of print]

**Klingmann C, Praetorius M, Baumann I, Plinkert PK**

Department of Otolaryngology, Head and Neck Surgery, University of Heidelberg, Heidelberg, Germany.

**Introduction:** Diving accidents affecting the inner ear are much more common than was once thought. Among the 319 patients treated in our clinic between January 2002 and November 2005, 46 cases involved 44 divers with symptoms of acute inner ear disorders. The objective of the present article is to investigate the symptoms of the acute disorders and assess any residual damage.

**Study design:** Retrospective case analysis.

**Materials and methods:** The medical records were used to study the cases of 18 divers treated for inner ear decompression illness on 20 occasions and 26 divers who had inner ear barotrauma. The symptoms of the disorder at the beginning of treatment, latency period before the first therapeutic measures, kind of initial therapy, symptoms after the accident, and hearing and balance functions at the last examination in our clinic were assessed. Divers with inner ear decompression illness were examined via means of transcranial or carotid Doppler ultrasonography for the presence of a vascular right-to-left (R/L) shunt.

**Results:** Of 18 divers with inner ear decompression illness, 17 reported vertigo as the main symptom. In one diver, the inner ear decompression illness was manifested bilaterally. The divers with inner ear decompression illness had been treated with hyperbaric oxygen therapy in 14 of 20 cases; the average latency period before the start of therapy was 40 hours (median, 10 h). In 15 (83%) of 18 patients, a large R/L shunt was detected, and in 14 (78%) of 18 patients, residual cochleovestibular damage was detected. Only 9 of 26 patients with inner ear barotrauma mentioned feeling dizzy, and in no patient was vertigo the main symptom. Twenty-one patients complained of tinnitus, whereas 20 complained of hearing loss. The hearing loss ranged from an unobtrusive difference of 10 dB between the ears up to complete deafness. Three patients were subjected to tympanoscopy because of suspected rupture of the round window membrane. Of patients with inner ear barotrauma, 78% had residual cochleovestibular damage.

**Conclusion:** We describe for the first time a patient with bilateral manifestation of inner ear decompression illness. Inner ear decompression illness is frequently associated with a R/L shunt; therefore, after a diving accident, the patient's fitness to dive should be assessed via a specialist in diving medicine. Both decompression illness and barotrauma of the inner ear result in residual cochleovestibular damage in more than three of four patients.
Hyperbaric oxygen in the treatment of sudden deafness.
Eur Arch Otorhinolaryngol. 2007 Mar 15; [Epub ahead of print]

Domachevsky L, Keynan Y, Shupak A, Adir Y
Israel Naval Medical Institute, IDF Medical Corps, P.O. Box 8040, 31 080, Haifa, Israel, liranura@bezeqint.net.

Currently, the treatment of sudden deafness (SD) is based mainly on complete bed rest and the administration of corticosteroids. Hyperbaric oxygen therapy (HBOT) has previously been suggested as adjunctive treatment. We describe two cases of successful HBOT for SD. The first patient presented with moderate mid-frequency hearing loss without accompanying symptoms, whereas the second patient had moderate low-frequency hearing loss with persistent tinnitus and a single episode of vertigo. HBOT in addition to conventional treatment soon after diagnosis resulted in full recovery of hearing in both patients. The pathogenesis of SD may involve a reduction in cochlear blood flow and perilymph oxygenation, making early HBOT a reasonable treatment modality for this condition.
Clinical Trials

Source: clinicaltrials.gov (17 April 2007)

The Effect of Tinnitus Retraining Therapy on Subjective and Objective Measures of Chronic Tinnitus

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<thead>
<tr>
<th>Current status</th>
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<tr>
<td>Sponsors and collaborators</td>
<td>Tinnitus Research Consortium</td>
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<td>Information provided by</td>
<td>Tinnitus Research Consortium</td>
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<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT00124800</td>
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<tr>
<td>Purpose</td>
<td>The objective of this study is to examine the efficacy of tinnitus retraining therapy (TRT) as a treatment of chronic tinnitus in people with limited hearing loss. The study design is prospective, randomized, double-blind, with repeated measures. The null hypothesis states there will be no difference in subjective measures of tinnitus severity between subjects treated with standard TRT and subjects treated with sham TRT.</td>
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<tr>
<td>Condition(s)</td>
<td>Tinnitus</td>
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<tr>
<td>Interventions</td>
<td>Behavior: Tinnitus retraining therapy</td>
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<tr>
<td></td>
<td>Device: Sound therapy</td>
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<td>Phase</td>
<td>Phase I</td>
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<td>Study type and design</td>
<td>Interventional, Treatment, Randomized, Double-Blind, Placebo Control, Parallel Assignment, Efficacy Study</td>
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<td>The Effect of Tinnitus Retraining Therapy on Subjective and Objective Measures of Chronic Tinnitus</td>
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<td>Further study details</td>
<td>Specific aims of the study are to:</td>
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<tr>
<td></td>
<td>- Evaluate the efficacy of TRT in reducing the objective magnitude of tinnitus.</td>
</tr>
<tr>
<td></td>
<td>- Evaluate the efficacy of TRT in reducing the subjective awareness and impact of tinnitus.</td>
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<tr>
<td></td>
<td>- Determine the therapeutic time course of improvement in tinnitus.</td>
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<td>- Determine the long-term improvement in tinnitus derived from TRT.</td>
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<td>Primary Outcomes</td>
<td>Change in objective measure of tinnitus loudness using psychoacoustic matching task; Change in subjective handicap rating of tinnitus using a standardized questionnaire</td>
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<td>Secondary Outcomes</td>
<td>Change in subjective ratings of tinnitus loudness, annoyance and awareness</td>
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<td>Expected completion</td>
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<td>Participants (age)</td>
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<tr>
<td><strong>Eligibility Inclusion Criteria</strong></td>
<td>Chronic non-pulsatile tinnitus</td>
</tr>
</tbody>
</table>
| **Eligibility Exclusion Criteria** | - Hyperacusis  
- Subjective hearing loss  
- Objective hearing loss with pure tone average greater than 35 dB sound pressure level (SPL)  
- Evidence of significant depression or suicidal ideation |
| **Overall contact** | David Pence BA  
Phone 217-545-7579  
dpence@siumed.edu |
| **Study chairs or principal investigators** | Carol A Bauer MD, Principal Investigator, Southern Illinois University School of Medicine |
| **Contact** | Carol Bauer MD  
Phone 217-545-5140  
cbauer@siumed.edu |
| **Locations** | **United States, Illinois**  
Southern Illinois University School of Medicine  
Springfield, Illinois, 62794, United States  
David Pence BA  
dpence@siumed.edu  
Carol A Bauer, MD, Principal Investigator |
| **Study ID Number** | 05-014 |
| **Last Updated** | 16 August 2005 |
| **Record first received** | 27 July 2005 |
| **ClinicalTrials.gov Identifier** | NCT00124800 |
| **Health Authority** | United States: Institutional Review Board |

### Brain Imaging of Tinnitus

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<th><strong>Current status</strong></th>
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<tbody>
<tr>
<td><strong>Sponsors and collaborators</strong></td>
<td>National Institute on Deafness and Other Communication Disorders (NIDCD)</td>
</tr>
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<td>National Institutes of Health Clinical Center (CC)</td>
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<tr>
<td><strong>ClinicalTrials.gov Identifier</strong></td>
<td>NCT00359931</td>
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<tr>
<td><strong>Purpose</strong></td>
<td>This study will use magnetic resonance imaging (MRI) to compare brain function in three groups of people: hearing-impaired people with tinnitus; hearing-impaired people without tinnitus; and people with normal hearing and without tinnitus. Also known as “ringing in the ears,” tinnitus is the false sensation of sounds.</td>
</tr>
</tbody>
</table>
| Condition(s) | Tinnitus, Hearing Loss  
Adults between 30 and 65 years of age who meet the following criteria may be eligible for this study:  
- Mild to moderate hearing loss who have experienced tinnitus daily for at least 1 year  
- Mild to moderate hearing loss who have never or rarely experienced tinnitus  
- Normal hearing who have never or rarely experienced tinnitus  
Candidates are screened with a medical history and questionnaires. Participants have a detailed hearing test to measure hearing and the nature of tinnitus. In a second visit, subjects have a brief physical examination, followed by MRI scanning. MRI uses a magnetic field and radio waves to produce images of body tissues and organs. For this procedure, the subject lies on a table that can slide in and out of the scanner (a narrow cylinder), wearing earplugs to muffle loud knocking and thumping sounds that occur during the scanning process. The subject may be asked to lie still for up to 8 minutes at a time. During the MRI, the subject performs computer-based tasks that involve listening to sounds. Another hearing test is done after the MRI.  

| Study type and design | Observational, Natural History, Cross-Sectional, Defined Population, Retrospective/Prospective Study  
| Official title | Neural Modeling and Brain Imaging of Tinnitus  
<p>| Further study details | Subjective tinnitus, the false perception of sound in the absence of an acoustic stimulus, occurs frequently as a consequence of noise-induced deafness. The purpose of this study is to investigate the brain sites and mechanisms underlying tinnitus using a combined mathematical modeling and functional brain imaging experimental approach. Although studies have focused on the neural bases of tinnitus, it is not known why tinnitus arises only in certain cases of hearing loss, and the contribution of different brain regions in tinnitus perception is poorly understood. This in turn, prevents the development of better studies and new treatment methods for tinnitus. The primary hypothesis is that a network of brain regions, from auditory processing areas to emotional processing areas, contributes to, and modulates, tinnitus perception. The brain imaging study will be used to study differences in the network of brain regions involved in listening and discriminating sounds for tinnitus sufferers as compared to a control group of subjects with similar hearing loss but without tinnitus. This comparison should permit the identification of brain regions most active in tinnitus. An age matched control group without hearing loss and tinnitus will be included to determine those effects due to hearing loss alone. The mathematical computational modeling will use a previously developed large-scale neural network model of auditory processing in the cerebral cortex, which will be modified to induce tinnitus via different neural mechanisms. The modeling study should allow us to evaluate the contribution of different cortical regions and mechanisms to tinnitus perception; some changes in the model will be more successful than others in inducing tinnitus and in matching simulated brain imaging data with experimental brain imaging data. The modeling study will use the same stimuli and experimental paradigm as the functional brain imaging study. Comparing the experimental and modeling results will provide hypotheses about the most likely mechanism mediating tinnitus. Together, the modeling and experimental studies will advance our knowledge of the brain regions and mechanisms underlying tinnitus. |</p>
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<th>Expected Total Enrollment</th>
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<td>Participants (age)</td>
<td>30 Years – 65 Years</td>
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<td>Gender</td>
<td>Both</td>
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</tbody>
</table>

### Eligibility inclusion criteria

**Plus Tinnitus Plus Hearing loss subjects.**
- Adults, between the ages of 30 to 65 years.
- Are able to hear and perceive sounds used in the experiment in the range 250 Hz to 2 KHz and have high-frequency sensorineural hearing loss beginning no lower than 2 KHz.
- In good health and not currently taking any medications regularly.
- Experience tinnitus daily.
- Have had non-pulsatile tinnitus for at least 1 year.
- Have bilateral or unilateral with unilateral dominance tinnitus.

**Minus Tinnitus Plus Hearing loss subjects.**
- Adults, between the ages of 30 to 65 years.
- Are able to hear and perceive sounds used in the experiment in the range 250 Hz to 2 KHz and have high-frequency sensorineural hearing loss beginning no lower than 2 KHz.
- In good health and not currently taking any medications regularly.
- Have never or rarely (i.e. transient episodes experienced by virtually everyone) experienced tinnitus.

**Minus Tinnitus Minus Hearing loss subjects or normal volunteers.**
- Adults, between the ages of 30 to 65 years.
- Have normal hearing.
- In good health and not currently taking any medications regularly

### Eligibility exclusion criteria

- Subjects with cognitive or neurological disorders, other than tinnitus.
- Subjects with hyperacusis or misophonia (hyper-sensitivity to loud noises).
- Subjects with mood disturbances such as depression or anxiety.
- Subjects with temporomandibular joint problems.
- Subjects with a history of significant medical disorders.
- Subjects with significant past and present history of hypertension, cardiovascular disease and diabetes mellitus or taking certain medications that cause change in blood volume/flow.
- Subjects with past or present neuropsychiatric illness, head trauma with loss of consciousness, epilepsy, seizures and other medical conditions that may alter cerebral functioning.
- Subjects who have pacemakers, aneurysm clips, metallic prostheses or shrapnel fragments.
- Subjects incapable of giving informed consent.
- Subjects with a positive pregnancy test.
- Children below the age of 18 years.
- Subjects who are not free of developmental disorders or who have a family history thereof.
- Subjects who are taking or have a history of taking recreational drugs or alcoholism.
- Subjects with unilateral or asymmetrical hearing loss who have not had (or cannot provide documentation of) comprehensive neuro-otologic workup will be excluded.

The exclusion criteria will be discussed with the subjects before their initial visit to NIH. Subjects will be counseled to refrain from caffeine four hours prior to audiological or MRI testing, refrain from using aspirin (or similar medications) for a few days prior to testing and to alert the investigators if they have been exposed to a loud noise within 24 hours prior to testing.
Patient Recruitment and Public Liaison Office
Phone (800) 411-1222
prpl@mail.cc.nih.gov
TTY 1-866-411-1010

Locations
United States, Maryland
National Institutes of Health Clinical Center, 9000 Rockville Pike, Bethesda, Maryland, 20892, United States; Recruiting

Study ID Number
060218; 06-DC-0218

Last Updated
24 February 2007

Record first received
2 August 2006

ClinicalTrials.gov Identifier
NCT00359931

Health Authority
United States: Federal Government

Psychophysiological Treatment of Chronic Tinnitus

Current status
recruiting

Sponsors and Collaborators
Philipps University Marburg Medical Center, German Research Foundation (Deutsche Forschungsgemeinschaft)

Information provided by
Philipps University Marburg Medical Center

ClinicalTrials.gov Identifier
NCT00397007

Purpose
The study aims to develop and to evaluate a psychophysiological intervention for distressing chronic tinnitus. Therefore 100 people suffering from chronic tinnitus are randomly assigned to either an intervention-group, receiving 12 sessions of a psychophysiological oriented intervention, or to a waiting-list-group, who are waiting for a comparable time period. Afterwards, patients of the waiting-list-group also receive intervention. The effects of the intervention on severity, distress and perceived loudness of the tinnitus as well as on other psychological variables like depression or self-efficacy are evaluated through comparing the results of the intervention group with those of the waiting-list-group.

Additionally the psychophysiological reactivity under different stress-conditions is measured before and after intervention or waiting. Therefore the activity of the muscles of head and shoulders (EMG) as well as the skin temperature and skin conductance are measured. It is hypothesized that patients with stronger psychophysiological reactivity benefit more from an psychophysiological intervention.

Condition(s)
Tinnitus

Interventions
Behavior: Biofeedback-based cognitive-behavioural intervention

Phase
Phase II

Study type and design
Interventional, Treatment, Randomized, Single Blind, Active Control, Parallel Assignment, Efficacy Study

Official title
Evaluation of Psychological and Psychophysiological Effects of a Biofeedback-Based Cognitive-Behavioral Psychotherapy for Chronic Tinnitus-Sufferers
The study aims to develop and to evaluate a psychophysiological intervention for distressing chronic tinnitus. Therefore 100 people suffering from chronic tinnitus are randomly assigned to either an intervention-group, receiving 12 sessions of a psychophysiological oriented intervention, or to a waiting-list-group, who are waiting for a comparable time period. Afterwards, patients of the waiting-list-group also receive intervention. The effects of the intervention on severity, distress and perceived loudness of the tinnitus as well as on other psychological variables like depression or self-efficacy are evaluated through comparing the results of the intervention group with those of the waiting-list-group.

Additionally the psychophysiological reactivity under different stress-conditions is measured before and after intervention or waiting. Therefore the activity of the muscles of head and shoulders (EMG) as well as the skin temperature and skin conductance are measured. It is hypothesized that patients with stronger psychophysiological reactivity benefit more from an psychophysiological intervention.

Further aims of the study are 1) to compare the muscle activity of the tinnitus-patients with those from healthy controls, because till now no study investigated if tinnitus-patients effectively present higher muscle activity in head and shoulders than healthy people and 2) to evaluate the influence of the subjective illness perceptions on the intervention-outcome, because it is hypothesized that patients with more somatic illness perceptions benefit more from a psychophysiological intervention than patients with rather psychological illness perceptions.

<table>
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<th>Primary Outcomes</th>
<th>Tinnitus Questionnaire German Version; Tinnitus diary</th>
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<tr>
<td>Secondary Outcomes</td>
<td>Symptom Check List; Beck Depression Inventory; Illness perception questionnaire; Pain disability index; Generalized self efficacy</td>
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<td>Expected Total Enrollment</td>
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<td>Study start</td>
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<td>Participants (age)</td>
<td>16 Years – 75 Years</td>
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<td>Gender</td>
<td>Both</td>
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</table>
| Eligibility inclusion criteria    | - 100 subjects with distressing and chronic tinnitus (for at least 6 month)  
- age: 16-75 years  
- sufficient language skills  
plus  
- 50 healthy control-subjects  
- without tinnitus or other hearing disease |
| Eligibility exclusion criteria    | tinnitus as a result of medical disease (e.g.Meniere's disease)  
attendance in the previous study  
psychosis or dementia |
| Contact recruiting                | Cornelia Weise, Dipl.-Psych  
Phone +49-6421-2825498  
weise@staff.uni-marburg.de |
| Study chairs or principal investigators | Winfried Rief, Dr.  
Phone +49-6421-2823641  
rief@staff.uni-marburg.de |
| Study ID Number                   | RI 574/12-1                                           |
**Vestipitant Or Vestipitant/Paroxetine Combination In Subjects With Tinnitus And Hearing Loss**

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<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT00394056</td>
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</tbody>
</table>

**Purpose**

Tinnitus associated to hearing loss is a high prevalent audiologic disorder with important unmet needs as far as therapy is concerned. The present study is exploring the possible beneficial effects on tinnitus loudness or annoyance of a combination drug treatment aimed to increase the local inhibitory activity of neural circuitries involved in sound perception and generation. Modest effects have been reported after 8-12 weeks treatment with antidepressants, including high dose paroxetine (up to 50 mg/day). Biologic data suggests that the combination of increase of extracellular serotonin using an SSRI and of blockade of NK1 receptors using a novel NK1 antagonist may lead to a reduced tinnitus and, possibly, improved hearing acuity. To this aim, two 14 day treatment conditions, i.e., SSRI paroxetine (20 mg/day) plus the NK1 antagonist vestipitant (25mg /day) or vestipitant alone (25 mg /day), will be compared to placebo in patients suffering from tinnitus previously selected for their capacity to reliably score the transient attenuation of tinnitus loudness produced by lidocaine infusion. Effects on principal endpoints will be collected within 4 hrs from last administration, when the plasma levels of vestipitant are calculated to be in the range associated to pharmacodynamic effects on VAS anxiety and qEEG (>30 ng/ml). PK, safety and tolerability of the paroxetine-vestipitant combination was addressed with preclinical and Phase I studies, showing no relevant issue. The cross-over study will require approximately 24 patients. Audiometry and computer-based Automated Psychoacoustics will be performed as instrumental endpoints to support subjective scores. A diary will be used at home to score tinnitus severity at home during the study.

**Condition(s)**

Tinnitus

**Interventions**

Drug: Vestipitant, Drug: Vestipitant + Paroxetine

**Phase**

Phase II

**Study type and design**

Interventional, Treatment, Randomized, Double-Blind, Placebo Control, Crossover Assignment, Efficacy Study

**Official Title**

Randomised, Double-Blind, Placebo Controlled, Cross-Over Study Comparing the Effects of Both Single Dose and Repeated Dosing Treatment for 14 Days of Vestipitant or Vestipitant / Paroxetine Combination in an Enriched Population of Subjects With Tinnitus & Hearing Loss
<table>
<thead>
<tr>
<th>Primary outcomes</th>
<th>Visual Analog Scales (VAS) to measure the change in tinnitus loudness as perceived at the moment of the measurement at 2 hrs after dosing (or at any other time point vs. pre-dose baseline).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expected Total Enrollment</td>
<td>24</td>
</tr>
<tr>
<td>Study start</td>
<td>October 2006</td>
</tr>
<tr>
<td>Participants (age)</td>
<td>18 Years – 60 Years</td>
</tr>
<tr>
<td>Gender</td>
<td>Both</td>
</tr>
<tr>
<td>Eligibility inclusion criteria</td>
<td>Subjects with a diagnosed tinnitus. Subject with THI severity grade of 3 or 4. Subjects willing to restrict alcohol intake. The subject must have given written consent. Women of childbearing potential who abstain from intercourse OR agree to birth control.</td>
</tr>
<tr>
<td>Eligibility exclusion criteria</td>
<td>- Subject with THI severity grade = 5 or less than or equal to 2. - Subject with pathologic level of anxiety or depression. - Subject with no audiogram deficit and with normal hearing. - Subjects that do not respond to the lidocaine infusion test or show a large variability in pre-infusion values. - Subjects with any serious medical disorder or condition that would preclude the administration of vestipitant or Paroxetine. - Existence of any surgical or medical condition which might interfere with the PK of the drug. - Subjects with hepatic impairment or a history of liver dysfunction. - Subjects with renal impairment. - Subjects positive for HIV, hepatitis C or hepatitis B. Subjects with abnormal laboratory, ECG or physical examination findings. - Subjects who are not euthyroid. - Subjects with a history of hepatic, cardiac, renal, neurologic, cerebrovascular, metabolic or pulmonary disease. - Subjects who have had a myocardial infarction. - Subjects with a history of seizure disorders. - Subjects with history of cancer. - Subjects with a history of drug or other allergy. - Subjects positive for drug use and/or a history of substance abuse or dependence. - Subjects who have taken psychotropic drugs or antidepressants within specified time frames. - Medication or foodstuff (e.g. grapefruit or grapefruit juice) which is known to interfere with liver enzymes. - The subject had a non-psychotropic medication with a serotonergic mechanism of action. - Subjects who have recently used an investigational drug or recently participated in a trial. - Subjects who have exhibited intolerance to NK1 antagonists or SSRIs. - Women who have a positive pregnancy test. - Female subjects who intend to get pregnant or male subjects who intend to father a child within the next 4 weeks following the last study drug administration in the study. - Subjects, who have donated a unit of blood or more within the previous month or who intend to donate blood within one month of completing the study.</td>
</tr>
</tbody>
</table>
Using PET-CT to Target and Validate Low-Frequency TMS as Treatment for Tinnitus

<table>
<thead>
<tr>
<th>Current status</th>
<th>recruiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsors and Collaborators</td>
<td>University of Arkansas, Tinnitus Research Consortium</td>
</tr>
<tr>
<td>Information provided by</td>
<td>University of Arkansas</td>
</tr>
<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT00329524</td>
</tr>
</tbody>
</table>

Purpose

One out of every five people experience tinnitus (a buzzing, ringing, or roaring sound in the ear) ranging from mild to severe impairment. To date there is no effective therapy that seems to help the tinnitus sufferer. The purpose of this study is to develop a therapy using a technique called Repetitive Transcranial Magnetic Stimulation (rTMS) to hopefully alleviate or reduce the symptoms of tinnitus. This research is being conducted at the University of Arkansas for Medical Sciences (UAMS). Twenty (20) right handed subjects, either males or females, 19-65 years of age, with tinnitus that is severe enough for those persons to seek medical attention will have been seen as patients in the UAMS Hearing and Balance Center, where routine testing includes a physical exam, hearing tests, evaluation of middle ear status, and an MRI scan (a machine that acquires visual images of the brain). A diagnosis of tinnitus will be established after ruling out all other possible causes of the tinnitus.

Condition(s)

Tinnitus

Interventions

Procedure: Repetitive Transcranial Magnetic Stimulation (rTMS)

Phase

Phase I

Study type and design

Interventional, Treatment, Non-Randomized, Open Label, Active Control, Single Group Assignment, Safety Study

Official Title

Using PET-CT to Target and Validate Low-Frequency TMS as Treatment for Tinnitus
**Further study details**

Subjects will be 20 right-handed patients (men and women), 19-65 years of age, with debilitating unilateral or bilateral tinnitus. All subjects must report experiencing the presence of their phantom auditory perception for at least 6 months and have a Tinnitus Handicap Questionnaire (THQ) score >30. Subjects will be recruited from the Otolaryngology Clinic at UAMS, where routine testing includes a physical exam; pure tone audiometry; and evaluation of middle ear status using tympanometry, stapedius reflex tests, and otoscopy. Patients will undergo a gadolinium-contrast MRI of the head to rule out acoustic neuroma or any other central nervous system pathology. All subjects will be thoroughly informed of the risks associated with the procedures in this study, as described in the Hazards to Subjects section, and written informed consent will be obtained. Subjects will be recruited for this study without regard to race or ethnicity.

**Primary Outcomes**

Determine if low-frequency rTMS improves tinnitus by decreasing cortical activity in the primary auditory cortex.

**Secondary Outcomes**

Determine if asymmetric cortical activation promotes attentional disturbance (variability); in patients with tinnitus.; Determine if rTMS treatment promotes lasting improvement in tinnitus patients.

**Expected Total Enrollment**

20

**Study start**

June 2006

**Participants (age)**

19 Years – 65 Years

**Gender**

Both

**Eligibility Inclusion Criteria**

- right-handed subjects
- 19-65 years of age
- debilitating unilateral or bilateral tinnitus
- Experiencing the presence of phantom auditory perception for >6 months
- Tinnitus Handicap Questionnaire score of >30

**Eligibility Exclusion criteria**

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

**Contact**

John Dornhoffer MD  
Phone 501-686-5016  
DornhofferJohnl@uams.edu

**Location**

United States, Arkansas  
University of Arkansas for Medical Sciences  
Little Rock, Arkansas, 72205, United States; Recruiting
John L Dornhoffer MD  
Phone 501-686-5016  
DornhofferJohnl@uams.edu
Brenda Speed  
Phone 501-686-5140  
SpeedBrendaO@uams.edu
Progressive Intervention Program for Tinnitus Management

Current status
Not yet recruiting

Sponsors and collaborators
Department of Veterans Affairs

Information provided by
Department of Veterans Affairs

ClinicalTrials.gov Identifier
NCT00371436

Purpose
The purpose of this multi-site randomized clinical study is to test a model treatment program in a VA Audiology clinic, to evaluate its efficacy, ease of implementation, and acceptability to audiologists.

Condition(s)
Tinnitus; Hearing Loss

Interventions
Procedure: Usual Care; Procedure: Tinnitus Progressive Management

Study Type and design:
Interventional, Treatment, Randomized, Open Label, Active Control, Parallel Assignment, Efficacy Study

Official Title
Progressive Intervention Program for Tinnitus Management

Further study details
The 2004 VA Annual Benefits Report reveals that tinnitus is the third most common individual service-connected disability in veterans. As of September 30, 2005, there were 339,573 veterans who had been awarded a service connection for their tinnitus, with annual compensation amounting to over $418,000,000 (Office of Policy and Planning, VA Central Office). In addition to being a major expense for VHA, tinnitus is a health care problem that is inadequately addressed at most VA medical centers. We have developed a research-based model of tinnitus clinical management that is designed for efficient implementation in VA Audiology clinics. The objective of the proposed study is to establish the model program at a VA Audiology clinic, and to evaluate its efficacy with veteran patients and its acceptability to audiologists.

The proposed study will be based at the NCRAR, and a prototype tinnitus management program will be established in the Audiology Clinic at the James A. Haley (Tampa) VA Medical Center. The program follows a five-level “progressive intervention” model that addresses the various needs of tinnitus patients in a systematic and hierarchical manner – from initial contact with a VA provider through long-term treatment. It is hypothesized that progressive intervention will result in a significant reduction in self-perceived tinnitus handicap relative to usual care.

During months 1-9, a comprehensive web-based tinnitus training course for audiologists will be developed, as well as a 20-page patient tinnitus-information booklet that uses principles of low health literacy. Six audiologists at the Tampa VA will participate, of which three will be randomly selected to complete the training course as preparation to conduct each of five levels of progressive intervention: (1) initial contact; (2) audiological assessment; (3) group educational counseling; (4) tinnitus evaluation; and (5) individualized treatment. The other three audiologists will not receive the training, and these “usual care” audiologists will essentially provide intervention levels 1 and 2.
Patients will be randomized to one of the six audiologists. All patients will complete outcomes questionnaires (Tinnitus Handicap Inventory [THI] and Veterans Short Form-36 health survey [SF-36V]) at baseline and 12 months (and at 24 months as resources permit). Outcomes of the THI will be compared between the two groups of patients to test the hypothesis. Data from the SF-36V will be used in secondary outcomes analyses. Each of the six audiologists will be interviewed informally and with a structured interview by the investigative team to determine their satisfaction with the tinnitus services that they provide, and how they feel they are meeting the needs of their patients. The three web-base-trained audiologists and the Service Chief will provide formative data to the Co-PI on an ongoing basis to monitor and adjust the program to achieve the best possible outcomes.

Development and evaluation of this prototype program will establish its practical utility for addressing the tinnitus needs of veterans in a comprehensive, yet efficient, fashion. If the study shows that the program is effective, the program could establish the standard for tinnitus management at all VA medical centers—meeting the needs of all veterans who have access to VA services.

### Primary Outcomes
Baseline questionnaire at 12 and 24 months for general tinnitus survey, the Tinnitus Handicap Inventory (THI.)

### Expected Total Enrollment
180

### Study start
October 2006

### Expected completion
September 2009

### Participants (Gender)
Both

### Eligibility inclusion criteria
Veterans who:
- Are outpatients at VA clinics in the vicinity of the James A. Haley VA Medical Center in Tampa, FL
- Have clinically significant tinnitus
- Have no significant language barrier
- Are capable of and willing to fulfill all study requirements

### Eligibility exclusion criteria
- Subjects must be free from any medical conditions that would interfere with study participation, e.g. medically or surgically treatable otologic disease; end-stage renal, pulmonary, or cardiovascular disease
- Patients undergoing chemotherapy or radiation treatment
- Patients with severe psychiatric disorders

### Contact
Christine Kaelin MBA  
Phone 503-220-8262 Ext. 57153  
christine.kaelin@va.gov

Tara Zaugg Au.D  
Phone 503-220-8262 Ext. 56608  
tara.zaugg@va.gov

### Location
**United States, Oregon**  
Portland VA Medical Center (648)  
Portland, Oregon, 97239, United States

James A Henry, PhD  
Phone 503-220-8262 Ext. 57466, james.henry@va.gov

Christine S Kaelin MBA  
Phone 503-220-8262 Ext. 57153, christine.kaelin@va.gov

### Study chairs or principal investigators
James A Henry, PhD, Principal Investigator, Research Scientist, National Center for Rehabilitative Auditory Research

### Study ID Number
C4488R

### Last Updated
1 November 2006

### Record first received
31 August 2006

### ClinicalTrials.gov Identifier
NCT00371436

### Health Authority
United States: Federal Government
Early Diagnosis of Steroid-Responsive & No-Responsive Hearing Loss

<table>
<thead>
<tr>
<th>Current status</th>
<th>recruiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsors and collaborators</td>
<td>Department of Veterans Affairs</td>
</tr>
<tr>
<td>Information provided by</td>
<td>Department of Veterans Affairs</td>
</tr>
<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT00013468</td>
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<tr>
<td>Purpose</td>
<td>Tinnitus is a prevalent issue for veterans who are proportionally more hearing-impaired than the civilian population. This study will be conducted as three concurrent projects designed to develop an efficient clinical technique to quantify tinnitus perception: (1) Laboratory development of the automated technique for comprehensive tinnitus quantification; (2) Development of a technique to test for tinnitus &quot;malingering&quot;; and (3) Evaluation of the automated technique in the clinical environment.</td>
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<tr>
<td>Condition(s)</td>
<td>Hearing Loss</td>
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<tr>
<td>Interventions</td>
<td>Procedure: Tinnitus</td>
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<td>Phase</td>
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<td>Study type and design:</td>
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<tr>
<td>Official Title</td>
<td>Early Diagnosis of Steroid-Responsive &amp; No-Responsive Hearing Loss</td>
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Further study details
Because of its close association with sensorineural hearing loss, tinnitus is a prevalent issue for veterans who are proportionally more hearing-impaired than the civilian population. The VA system disburses $110 million per year to over 115,000 veterans for their service-connected tinnitus disability, thus it is clearly a problem for veterans and for the VA. Unfortunately, most VAMCs do not have systematic clinical care available for their veterans suffering from tinnitus. The most obvious needs are to develop effective treatment methodologies for veterans, and to standardize a procedure for quantifying the disorder. Each of these concerns is a focus of this laboratory, and the present proposal addresses the latter need as a continuation study to develop reliable techniques to measure tinnitus.

The goal of this proposed study is a fully functional system, documented for response reliability and ready for clinical implementation at VA audiology clinics outside of Portland. To achieve that end goal, the study will be conducted as three concurrent projects: (1) Further laboratory development of the automated technique for comprehensive tinnitus quantification; (2) Development of a technique to test for tinnitus "malingering"; and (3) Evaluation of the automated technique in the clinical environment.

For Project 1, a series of experiments is proposed to reduce the time of testing, and to add new measurement capabilities. Each experiment will involve specification, design, and implementation of program modifications, human subject testing, analysis of results, and further modifications as indicated. Another series of experiments (Project 2) will be conducted to develop a tinnitus malingering exam. With such a test, veterans with true tinnitus would provide reliable responses, while those feigning tinnitus would have difficulty responding reliably. For Project 3, a duplicate measurement system will be installed at the Portland VA Regional Tinnitus Clinic. The automated technique will be used to quantify tinnitus in veteran patients during their tinnitus evaluation.
Patients will be invited to return for repeat testing, which will provide reliability data for clinical responses. This project will promote clinical feedback that will be important for final development of the system as a clinical tool. The three projects outlined above are designed to develop an efficient clinical technique to quantify tinnitus perception. Because the technique is computer automated, its implementation at VA clinics will involve a minimum of training and expenditure. The technique is further expected to impact the medical care of non-VA clinics, and could

<table>
<thead>
<tr>
<th>Expected Total Enrollment</th>
<th>50</th>
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<tr>
<td>Study start</td>
<td>August 2000</td>
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<tr>
<td>Expected completion</td>
<td>August 2003</td>
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<tr>
<td>Participants (age)</td>
<td>18 Years and above</td>
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<tr>
<td>Gender</td>
<td>Both</td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>Hearing impaired</td>
</tr>
<tr>
<td>Contact</td>
<td>Steven Hefeneider PhD Phone 503 220-3428 <a href="mailto:hefeneid@ohsu.edu">hefeneid@ohsu.edu</a></td>
</tr>
<tr>
<td>Location</td>
<td>United States, Oregon VAMC, Portland Portland, Oregon, United States; Recruiting Steven Hefeneider PhD Phone 503-220-3428</td>
</tr>
<tr>
<td>Study chairs or principal investigators</td>
<td>John Fryer, Ph.D., Asst. Director, Department of Veterans Affairs, Program Analysis and Review Section (PARS), Rehabilitation Research &amp; Development Service Nancy Rocheleau, Program Analyst, Department of Veterans Affairs, Program Analysis and Review Section (PARS), Rehabilitation Research &amp; Development Service</td>
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<td>Last Updated</td>
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<td>Record first received</td>
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<td>ClinicalTrials.gov Identifier</td>
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<td>Health Authority</td>
<td>United States: Federal Government</td>
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**Clinical Applications for Time-Compressed Speech Tests**

<table>
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<tr>
<th>Current status</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Sponsors and collaborators</td>
<td>Department of Veterans Affairs</td>
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<tr>
<td>Information provided by</td>
<td>Department of Veterans Affairs</td>
</tr>
<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT00371839</td>
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<tr>
<td>Purpose</td>
<td>The purpose of this study is to determine the effects of age-related cognitive changes on hearing aid benefit based on hearing aid compression time constants. The hypothesis is that people with poor working memory skills will benefit from slow time constants in hearing aid compression while those with good working memory skills will be able to benefit from more sophisticated compression algorithms with rapid time constants.</td>
</tr>
</tbody>
</table>
Condition(s) | Hearing Loss
---|---
Interventions | Procedure: Initial Contact  
Procedure: Audiological Evaluation  
Procedure: Group Education  
Procedure: Tinnitus Evaluation  
Procedure: Individualized Treatment
Study type and design: | Interventional, Treatment, Randomized, Open Label, Active Control, Single Group Assignment, Efficacy Study
Official Title | Clinical Applications for Time-Compressed Speech Tests
Further study details | Recent research has shown the relevance of cognitive function in hearing aid evaluation and the sensitivity of the aging auditory system to temporal distortions. The proposed investigation will examine the interaction of working memory and hearing aid compression method on speech recognition in background competition for older listeners. This interaction will be investigated for the following three forms of background competition:
1. Competition from continuous speech-shaped noise.
2. Competition from speech-modulated noise.
3. Competition from a single interfering talker.
The goals of the study will be accomplished in two phases. In the first phase, 160 adults aged 50 through 75 years will be evaluated on a battery of tests to determine their cognitive capacity, time-compressed speech scores and their candidacy for inclusion in the second phase of the study. At the conclusion of this phase of testing, the participants will be divided into three groups:
1. subjects with TCS test scores in the highest quartile (the HIGH group)  
2. subjects with TCS test scores in the lowest quartile (the LOW group)  
3. the remaining listeners
The second phase of the experiment will include listeners from the HIGH and LOW groups only. These subjects will be evaluated with respect to their speech recognition ability for three types of interference (steady-state noise, speech-modulated noise, single interfering talker). The HINT test (Nilsson, Soli, & Sumida, 1995; Nilsson et al., 1994) will be used to obtain the signal-to-noise ratio (SNR) at 50% recognition for the three masking conditions for each of three types of amplification:
1. one-channel linear amplification (LINEAR) with frequency shaping  
2. two-channel wide dynamic range compression with fast time constants (FAST)  
2-channel wide dynamic range compression with slow time constants (SLOW)  
Listener groups will be compared across hearing aid conditions and across background interference conditions.
Primary Outcomes | Groups of high and low scores on the time-compressed speech test will be compared on other measures – cognitive tests, hearing aid speech recognition tests in various background interference at the end of the study. The outcome will benefit audiology cl
Secondary Outcomes | Verification of time-compressed speech test as an appropriate clinical tool for hearing aid evaluations with older clients
Expected Total Enrollment | 160
Study start | September 2006
Expected completion | June 2009
Participants (age) | 50 Years – 75 Years
<table>
<thead>
<tr>
<th>Gender</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligibility inclusion criteria</td>
<td>Participants will be 50 to 75 years old. Hearing loss will be limited to 40 dB HL from 250 Hz through 1000 Hz, and to 60 dB HL through 4000 Hz. Hearing loss must be greater than 25 dB at two or more frequencies from 250 to 4000 Hz.</td>
</tr>
<tr>
<td>Eligibility exclusion criteria</td>
<td>None of the participants will be current or past hearing aid users; all will be free of ear disease. Participants with conductive hearing losses, defined as air-bone gap greater than 15 dB, will be excluded. The audiometric battery with acoustic reflex thresholds and decay measurements will be used to exclude anyone with evidence of a central disorder or a pathology other than a sensorineural loss. Those potential participants will be referred to a medical professional.</td>
</tr>
</tbody>
</table>
| Contact                 | Nancy Vaughan PhD  
Phone 503.220.8262 |
| Location                | United States, Oregon  
Portland VA Medical Center  
Portland, Oregon, 97239, United States  
Bonnie Becker  
Phone 503-220-8262 Ext. 54525  
Bonnie.becker@med.va.gov  
Izumi Furukawa  
Phone 503.220.8262 Ext. 54525  
izumi.furukawa@med.va.gov  
Nancy Vaughan PhD, Principal Investigator |
| Study chairs or principal investigators | Nancy E Vaughan PhD, Principal Investigator, Research Scientist, National Center for Rehabilitative Auditory Research |
| Study ID Number         | C4338R |
| Last Updated            | 8 September 2006 |
| Record first received   | 31 August 2006 |
| ClinicalTrials.gov Identifier | NCT00371839 |
| Health Authority        | United States: Federal Government |

### Safety and Efficacy of Intratympanic Application of Dexamethasone Via Catheter in Patients With Sudden Hearing Loss

<table>
<thead>
<tr>
<th>Current status</th>
<th>recruiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsors and collaborators</td>
<td>University Hospital Tuebingen</td>
</tr>
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<td>Information provided by</td>
<td>University Hospital Tuebingen</td>
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<td>ClinicalTrials.gov Identifier</td>
<td>NCT00335920</td>
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<tr>
<td>Purpose</td>
<td>The purpose of this study is to evaluate the efficacy and safety of an intratympanic continuous two-week application of dexamethasone compared to placebo using a temporarily implanted catheter in patients with severe to profound sudden sensorineural hearing loss and insufficient recovery after initial systemic prednisolone therapy.</td>
</tr>
<tr>
<td>Condition(s)</td>
<td>Sudden Deafness</td>
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<tr>
<td>Interventions</td>
<td>Drug: Dexamethasone-dihydrogenphosphate (4mg/ml)</td>
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Phase III

Study type and design: Interventional, Treatment, Randomized, Double-Blind, Placebo Control, Parallel Assignment, Safety/Efficacy Study

Official Title
A Prospective, Randomized, Double Blind, Placebo Controlled, Multicenter Study on the Safety and Efficacy of Continuous Infusion of Corticosteroid Delivered Via Catheter in Patients With Idiopathic Sudden Sensorineural Hearing Loss

Further study details
Patients suffering from unilateral severe to profound sudden sensorineural hearing loss (ISSNHL) or anacusis with no or insufficient recovery after 12-21 days after onset will be treated for 14 days with Dexamethasone or placebo delivered intratympanically via a micro-catheter temporarily implanted into the round window niche and an external mini-pump.

Due to the relatively unknown risks of intratympanic treatment by catheter implantation, a significant spontaneous recovery rate and an existing standard therapy for ISSNHL in Germany (systemic glucocorticoids), patients will only be enrolled into the study if no or insufficient recovery of hearing threshold could be observed after initial systemic therapy.

The study will be carried out until 10 patients per group have been randomized regardless in which study center they have been randomized. After the last patient of these 10 patients per group has reached the endpoint an interim analysis will be done. The statistical estimation of the total number of subjects to be randomized will be completed after this interim analysis by the responsible statistician.

Primary Outcomes
Pure tone audiometric threshold

Secondary Outcomes
Word recognition (speech audiometry); tinnitus improvement; adverse events (worsening of hearing and/or vertigo and/or tinnitus, middle ear inflammation, pain)

Expected Total Enrollment
26

Study start
October 2003

Participants (age)
18 Years – 75 Years

Gender
Both

Eligibility inclusion criteria
- Signed informed consent form
- Age is greater than 18 years old and less than 75 years old.
- Diagnosis of unilateral Idiopathic sudden sensorineural hearing loss (i.e. sudden sensorineural hearing loss of unknown etiology)
- Sensorineural hearing loss is at least 50 dB or more for three or more frequencies in standard pure tone, bone-conducted audiogram within the range of 500 Hz to 4000 Hz (500, 1000, 2000, 3000 and 4000), 60 dB or more for two of these frequencies or 70 dB or more for any frequency within this range, or a decrease in the SRT to 70 dB or greater (not accounted for by conductive hearing loss) or a drop in speech discrimination score to less than or equal to 30%
- Hearing loss occurred within 72 hours
- Hearing loss occurred at least 12 days ago but less than or equal to 21 days ago
- Insufficient recovery of the ISSNHL at least 12 days after onset whether or not the patient received Local Standard Therapy (i.e. Hearing in the contralateral ear is at least 20 dB better than the affected ear in at least three frequencies (any three of 500, 1000, 2000, 3000, 4000 Hz))
### Eligibility exclusion criteria

- Age is less than 18 or greater than 75 years old
- Hearing loss occurred less than 12 days or more than 21 days ago
- Positive pregnancy test, risk of pregnancy (insufficient protection or lactation)
- Middle ear inflammation or effusion
- Ear canal inflammation
- Conductive hearing loss of greater than 10 dB
- Sudden bilateral hearing loss
- Presence of any conditions or symptoms which indicate that the hearing loss is not ISSNHL, for example, acoustic trauma, Meniere’s disease, fluctuating hearing loss, endolympathic hydrops, suspected retro-cochlear lesion, hearing loss due to ear surgery, perilymph fistula or barotrauma.
- Pulse synchronic tinnitus (potentially due to glomus jugulare tumor)
- Previous otologic surgery (excluding ventilation tubes)
- History in the past 6 months of ototoxic treatment such as chemotherapy, use of loop diuretics, high dose aspirin, etc.
- Known hypersensitivity, allergy or intolerance to the study medication or any history of severe abnormal drug reaction
- Use of non-permitted treatment during the study
- Intake of experimental drugs or participation in a clinical study within the last 30 days
- Only hearing ear
- History of drug abuse or alcoholism
- History of an ischemic disorder (previous strokes, previous heart attacks, peripheral arterial occlusion disease)
- Patient is not capable of understanding the informed consent form (whether due to its language or for other reasons)
- Any psychiatric syndrome requiring treatment with neuroleptics, antidepressants, hypnotics or anxiolytics which has/have been prescribed within three months preceding inclusion into the study and/or cannot be continued at the same dose during the study
- Any severe (systemic) neurological disease (e.g. Epilepsy, Parkinson’s disease, Dementia/Alzheimer’s disease, Multiple sclerosis)
- Any reason, in the investigator’s opinion, that prohibits inclusion into the study

### Contact

**Stefan K Plontke M.D.**
Phone +49 7071 29- Ext. 88188
Stefan.Plontke@uni-tuebingen.de

**Hans-Peter Zenner M.D.**
Phone +49 7071 29- Ext. 88001
Zenner@uni-tuebingen.de

### Location

**Germany**
Department of Otorhinolaryngology, University of Tubingen
Tubingen, 72076, Germany; Recruiting
- Hans-Peter Zenner, M.D., Principal Investigator
  Stefan K Plontke, M.D., Sub-Investigator
  Assen Koitschev, M.D., Sub-Investigator
  Hubert Lowenheim, M.D., Sub-Investigator
  Serena Preyer, M.D., Sub-Investigator
  Rainer Zimmermann, M.D., Sub-Investigator
St. Vincentius Kliniken, Klinik für HNO Heilkunde
Karlsruhe, 76042, Germany; Recruiting
- Jurgen Mertens, M.D., Principal Investigator
  Andreas Weidner, M.D., Sub-Investigator
Bundeswehrkrankenhaus Ulm, Ulm, 89081, Germany; Terminated
Multi-Site Randomized Clinical Study of Tinnitus Treatment Methods

<table>
<thead>
<tr>
<th>Current status</th>
<th>No longer recruiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsors and collaborators</td>
<td>Department of Veterans Affairs</td>
</tr>
<tr>
<td>Information provided by</td>
<td>Department of Veterans Affairs</td>
</tr>
<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT00235807</td>
</tr>
</tbody>
</table>

**Purpose**
The purpose of this multi-site randomized clinical study is to assess treatment outcomes for three forms of tinnitus treatment: Tinnitus Retraining Therapy (TRT), Tinnitus Masking, and Comprehensive Audiological Tinnitus Treatment (CATT). There are four study sites: VAMC Audiology Clinics at Bay Pines, FL; Portland, Seattle and San Diego. Thirty-six subjects (veterans) are enrolled into treatment at each site – 12 into each treatment group. Each subject will receive 18 months of treatment. Treatment appointments and outcome questionnaires will occur at 0, 3, 6, 12, and 18 months. Questionnaires will also be completed by mail and by telephone at 30 months. Qualified subjects were initially randomized to one of the treatment groups or to a 6-month Waiting List group. Those in the Waiting List group complete outcome questionnaires at 3 and 6 months, and are randomized into one of the three treatment groups. They then receive 18 months of treatment as above.

**Condition(s)**
Tinnitus

**Interventions**
- Procedure: Tinnitus Masking
- Procedure: Tinnitus Retraining Therapy (TRT)
- Procedure: Comprehensive Audiological Tinnitus Treatment (CATT)

**Study type and design:**
Interventional, Treatment, Randomized, Open Label, Active Control, Parallel Assignment, Efficacy Study

**Official Title**
Multi-Site Randomized Clinical Study of Tinnitus Treatment Methods

**Further study details**
Although tinnitus is especially problematic for veterans, the DVA has no established protocol for tinnitus rehabilitation. We recently completed a randomized clinical trial to evaluate the efficacy of tinnitus treatment for veterans. Tinnitus Masking and Tinnitus Retraining Therapy (TRT) were both shown to be effective for the majority of veterans treated with these methods by “expert” tinnitus clinicians.
Further study details

The objective of the present study is to determine if the same level of treatment efficacy observed in the previous study can be obtained by “typical” VA audiologists in their clinical environment. In addition, a third group has been added, called Comprehensive Audiological Tinnitus Treatment (CATT), which will serve as a control group for nonspecific effects of treatment using a standardized protocol of hearing aids and education.

Veterans with clinically significant tinnitus were recruited to receive treatment with Masking, TRT, or CATT in Audiology Clinics at the Bay Pines, Portland, San Diego, and Seattle VAMCs. There are three Treatment Audiologists at each of the sites, one for each of the three treatment methods. Each method uses a variation of “sound therapy” and of educational counseling. Sound therapy involves the use of wearable ear-level devices, including sound generators (“maskers”), hearing aids, or combination devices (hearing aid and masker combined). Only the CATT group is restricted to the use of hearing aids only (note: CATT subjects who do not require hearing aids are the only subjects in this study who do not receive ear-level devices). TRT uses a structured counseling protocol that teaches concepts that are unique to TRT. The Masking protocol has been created to match the TRT counseling with respect to comparable formatting and length of counseling sessions, but containing information specific to the concepts of Masking. The CATT counseling protocol is similarly matched in format and length, but the information conveyed is of a more generic nature (general audiologic counseling information).

Assessment of outcomes will utilize questionnaires that are administered at intervals before, during, and after the 18 months of treatment.

Potential participants at all sites were telephone-screened by the Project Audiologist in Portland to determine if the tinnitus is a clinically significant problem warranting 18 months of treatment. Veterans who passed the screening were scheduled to meet with the Research Coordinator (RC) at the respective study site. At this first visit, veterans were consented, completed questionnaires and were then informed as to their group placement. Per a randomization schedule, they were placed into one of the three treatment groups, or into the 6-month waiting list group (with treatment starting 6 months later). At the initial evaluation with the respective Treatment Audiologist, a tinnitus verbal interview was administered, hearing and tinnitus testing were performed, and ear mold impressions were taken to order the custom ear-level devices. The veteran returned approximately 3-4 weeks later to be fitted with the devices and to receive the counseling/education that initiates treatment. Subjects return for follow-up treatment at 3, 6, 12 and 18 months. At the follow-up appointments, the RC collects and checks the questionnaires, and the Treatment Audiologist administers the follow-up verbal interview and repeats the counseling protocol. One year following treatment, the Project Audiologist will mail out written questionnaires that will be returned by mail, and will telephone the subjects to repeat the follow-up verbal interview.

Primary Outcomes

| Tinnitus Severity Index (TSI), Tinnitus Handicap Inventory, Tinnitus Handicap Questionnaire and Tinnitus Interview forms. These are administered at baseline, as well as at 3, 6, 12 and 18 months. |

Expected Total Enrollment 144

Study start June 2004

Study completion November 2006

Participants (age) 21 Years – 80 Years
Evaluation of Treatment Methods for Clinically Significant Tinnitus

<table>
<thead>
<tr>
<th>Current status</th>
<th>No longer recruiting</th>
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</thead>
<tbody>
<tr>
<td>Sponsors and collaborators</td>
<td>Department of Veterans Affairs</td>
</tr>
<tr>
<td>Information provided by</td>
<td>Department of Veterans Affairs</td>
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<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT00013390</td>
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<tr>
<td>Purpose</td>
<td>The investigators propose to evaluate two different approaches to the alleviation of tinnitus symptoms by comparing changes from baseline performance on the Tinnitus Severity Index. They propose to provide an unbiased evaluation of competing methodologies. The design is one in which pairs of prospective subjects are randomly assigned to one of two treatment groups. Changes in group performance will be compared for selected measures.</td>
</tr>
<tr>
<td>Condition(s)</td>
<td>Tinnitus</td>
</tr>
<tr>
<td>Interventions</td>
<td>Procedure: Tinnitus</td>
</tr>
<tr>
<td>Phase</td>
<td>Phase II</td>
</tr>
<tr>
<td>Study type and design:</td>
<td>Intervventional, Treatment, Randomized, Open Label, Active Control, Single Group Assignment, Efficacy Study</td>
</tr>
<tr>
<td>Official Title</td>
<td>Evaluation of Treatment Methods for Clinically Significant Tinnitus</td>
</tr>
<tr>
<td>Expected Total Enrollment</td>
<td>200</td>
</tr>
<tr>
<td>Study start</td>
<td>October 1999</td>
</tr>
<tr>
<td>Study completion</td>
<td>September 2002</td>
</tr>
</tbody>
</table>
The Effect of Gabapentin on the Sensation and Impact of Tinnitus

- **Sponsors and collaborators**: Tinnitus Research Consortium
- **Information provided by**: Tinnitus Research Consortium
- **ClinicalTrials.gov Identifier**: NCT00257270
- **Purpose**: This study evaluated the effectiveness of gabapentin in treating tinnitus in two populations: Tinnitus with associated acoustic trauma and tinnitus without associated acoustic trauma. The hypothesis was that gabapentin would decrease both subjective and objective features of tinnitus in the trauma group, but would be less effective in the non-trauma group.
- **Condition(s)**: Tinnitus
- **Interventions**: Tinnitus
- **Phase**: Phase II
- **Study type and design**: Interventional, Treatment, Non-Randomized, Single Blind, Placebo Control, Crossover Assignment, Efficacy Study
- **Official Title**: The Effect of Gabapentin on the Sensation and Impact of Tinnitus
- **Further study details**: **Methods**: A prospective, placebo-controlled, single-blind study of the effect of gabapentin on tinnitus was employed. Audiograms and personal histories were used to categorize tinnitus etiology as either secondary to acoustic trauma, or not associated with acoustic trauma. Participants were restricted to those with moderate-to-severe tinnitus for at least one year. All participants received gabapentin in a graduated ascending-descending dose series over 20 weeks (peak dose of 2400 mg/day).
  **Results**: There was a significant improvement in tinnitus annoyance for the trauma group (p = 0.05). Other subjective aspects of tinnitus were not significantly affected in either group. Between-subject variability of therapeutic response was considerable.
Nevertheless, considering subjective loudness ratings, 4/19 non-trauma participants, and 6/20 trauma participants showed an improvement of 20 percent or better. Considering psychoacoustic loudness estimates, 4/19 non-trauma and 6/20 trauma participants showed a 15 dB (HL) improvement. Evenly dividing each group into high and low responders revealed significant improvement in loudness at 1800 and 2400 mg/day for the trauma high-response subgroup (p = 0.007). No significant improvement was obtained for other subgroups.

<table>
<thead>
<tr>
<th>Primary Outcomes</th>
<th>Psychophysical loudness match of tinnitus to broad band noise and pure tones.; Subjective evaluation of tinnitus impact using Tinnitus Handicap Questionnaire.; The subjective and objective measures were obtained after treatment with placebo and 4 doses of gabapentin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary Outcomes</td>
<td>Quality of Life survey (SF36-QOL)</td>
</tr>
<tr>
<td>Expected Total Enrollment</td>
<td>40</td>
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<tr>
<td>Study start</td>
<td>August 2003</td>
</tr>
<tr>
<td>Study completion</td>
<td>January 2005</td>
</tr>
<tr>
<td>Participants (age)</td>
<td>18 Years – 75 Years</td>
</tr>
<tr>
<td>Gender</td>
<td>both</td>
</tr>
</tbody>
</table>
| Eligibility inclusion criteria | - non-pulsatile tinnitus present > 1 year  
- Tinnitus Handicap Questionnaire score > 30  
- ability to perform psychophysical matching procedure |
| Eligibility exclusion criteria | - evidence of depression  
- renal insufficiency  
- conductive hearing loss |
| Study chairs or principal investigators | Carol Bauer, MD, Principal Investigator, Southern Illinois University School of Medicine |
| Study ID Numbers | 03-073 |
| Last Updated | November 18, 2005 |
| Record first received | November 18, 2005 |
| ClinicalTrials.gov Identifier | NCT00257270 |
| Health Authority | United States: Institutional Review Board |

**Gabapentin for the Treatment of Tinnitus**

<table>
<thead>
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<th>Current status</th>
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<tbody>
<tr>
<td>Sponsors and collaborators</td>
<td>National Institute on Deafness and Other Communication Disorders (NIDCD)</td>
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<tr>
<td>Information provided by</td>
<td>National Institute on Deafness and Other Communication Disorders (NIDCD)</td>
</tr>
<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT00317850</td>
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</table>

**Purpose**

The specific aim of the Gabapentin for the Relief of Idiopathic Subjective Tinnitus Trial is to assess the therapeutic benefit of Gabapentin (Neurontin®) for subjective idiopathic troublesome tinnitus. We employed a double-blind placebo-controlled randomized clinical trial design to assess the efficacy of Gabapentin. Adults, between the ages of 18 and 70 with idiopathic, subjective, troublesome, unilateral or bilateral, non-pulsatile tinnitus of 6 month’s duration or greater and score of 38 or greater on the Tinnitus Handicap Inventory were enrolled.
<table>
<thead>
<tr>
<th>Condition(s)</th>
<th>Tinnitus</th>
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<tbody>
<tr>
<td>Interventions</td>
<td>Drug: Gabapentin (Neurontin)</td>
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<tr>
<td>Phase</td>
<td>Phase II, Phase III</td>
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<tr>
<td>Study type and design:</td>
<td>Interventional, Treatment, Randomized, Double-Blind, Placebo Control, Parallel Assignment, Efficacy Study</td>
</tr>
<tr>
<td>Official Title</td>
<td>Gabapentin for the Relief of Idiopathic Subjective Tinnitus</td>
</tr>
<tr>
<td>Primary Outcomes</td>
<td>Tinnitus Handicap Inventory Score from Baseline to Week 8</td>
</tr>
<tr>
<td>Secondary Outcomes</td>
<td>Beck Depression Inventory Score from Baseline to Week 8; Brief Symptom Inventory Score from Baseline to Week 8; Epworth Sleepiness Scale Score from Baseline to Week 8</td>
</tr>
<tr>
<td>Expected Total Enrollment</td>
<td>160</td>
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<tr>
<td>Study start</td>
<td>April 2004</td>
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<tr>
<td>Study completion</td>
<td>February 2006</td>
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<tr>
<td>Participants (age)</td>
<td>18 Years – 70 Years</td>
</tr>
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<td>Gender</td>
<td>Both</td>
</tr>
<tr>
<td>Eligibility inclusion criteria</td>
<td>Adults, between the ages of 18 and 70</td>
</tr>
<tr>
<td></td>
<td>Idiopathic, subjective, troublesome, unilateral or bilateral, non-pulsatile tinnitus (ICD-9 --388.31) of 6 month's duration or greater</td>
</tr>
<tr>
<td></td>
<td>Tinnitus handicap score of 38 or greater on the Tinnitus Handicap Inventory</td>
</tr>
<tr>
<td>Eligibility exclusion criteria</td>
<td>The symptoms of tinnitus can be affected by the concomitant use of tricyclic antidepressants, carbamazepine, phenytoin, valproate sodium, or benzodiazepines. Patients who have used these drugs within 30 days of screening will not be enrolled.</td>
</tr>
<tr>
<td></td>
<td>Impaired renal function as determined from serum creatinine levels, using the following formulas35: adult male Ccr = (140 - age) X weight in kilograms/(72 X serum creatinine in milligrams per deciliter); and adult female Ccr = [(140 - age) X weight in kilograms/(72 X serum creatinine in milligrams per deciliter)] X 0.85, where Ccr indicates creatinine clearance.</td>
</tr>
<tr>
<td></td>
<td>Patients with tinnitus related to cochlear implantation, retrocochlear lesion, or other known anatomic/structural lesions of the ear and temporal bone</td>
</tr>
<tr>
<td></td>
<td>Patients with any serious or unstable medical or psychiatric condition.</td>
</tr>
<tr>
<td></td>
<td>Patients whose ability to give informed consent is in question.</td>
</tr>
<tr>
<td>Study chairs or principal investigators</td>
<td>Jay F Piccirillo, MD, Principal Investigator</td>
</tr>
<tr>
<td></td>
<td>Washington University School of Medicine</td>
</tr>
<tr>
<td>Study ID Numbers</td>
<td>R01 DC006253-01</td>
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<tr>
<td>Last Updated</td>
<td>12 May 2006</td>
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<td>Record first received</td>
<td>21 April 2006</td>
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<td>Health Authority</td>
<td>United States: Federal Government</td>
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**Neramexane for Tinnitus**

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<th>Current Status</th>
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<tr>
<td>Sponsors and collaborators</td>
<td>Merz Pharmaceuticals GmbH</td>
</tr>
<tr>
<td>Information provided by</td>
<td>Merz Pharmaceuticals GmbH</td>
</tr>
<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT00405886</td>
</tr>
<tr>
<td>Purpose</td>
<td>Tinnitus is commonly referred to as “ringing of the ears” – the perception of sounds in the absence of an external source of acoustic signals. Tinnitus may represent a severe disease and symptoms include depression, sleeping difficulties, decreased sound tolerance and hearing loss. One hypothesis is that tinnitus is caused by an increased activity of NMDA glutamate and dysfunctional alpha9/alpha10 acetylcholine receptors in the inner ear and central nervous system. Neramexane may alleviate tinnitus symptoms due to its NMDA and alpha9/alpha10 nACh receptor blocking activity. The purpose of this study is to assess the safety and efficacy of Neramexane compared with placebo in patients with subjective tinnitus.</td>
</tr>
<tr>
<td>Condition(s)</td>
<td>Tinnitus</td>
</tr>
<tr>
<td>Interventions</td>
<td>Drug: Neramexane</td>
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<tr>
<td>Phase</td>
<td>Phase II</td>
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<tr>
<td>Study type and design</td>
<td>Interventional, Treatment, Randomized, Double-Blind, Placebo Control, Parallel Assignment, Safety/Efficacy Study</td>
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<tr>
<td>Official Title</td>
<td>A Randomised, Double-Blind, Placebo-Controlled, Clinical Dose-Ranging Trial to Evaluate Efficacy and Safety of a NMDA Antagonist for Oral Administration in Patients With Subjective Tinnitus</td>
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<tr>
<td>Primary Outcomes</td>
<td>Change from baseline in tinnitus severity at the endpoint visit</td>
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<tr>
<td>Expected Total Enrollment</td>
<td>400</td>
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<tr>
<td>Study start</td>
<td>October 2005</td>
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<tr>
<td>Participants (age)</td>
<td>18 Years – 65 Years</td>
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<tr>
<td>Gender</td>
<td>Both</td>
</tr>
<tr>
<td>Eligibility inclusion criteria</td>
<td>main inclusion criterion: persistent, subjective, uni- or bilateral tinnitus</td>
</tr>
<tr>
<td>Eligibility exclusion criteria</td>
<td>main exclusion criterion: intermittent or pulsatile tinnitus</td>
</tr>
</tbody>
</table>
| Location                        | Austria  
Vienna, Austria  
Germany  
Munich, Germany |
| Study chairs or principal investigators | Markus Suckfüll, MD PhD Ass. Prof., Study Chair  
Ludwig-Maximilian-University of Munich |
| Study ID Numbers                | MRZ 92579-0508/1 |
| Last Updated                    | 7 December 2006 |
| Record first received           | 29 November 2006 |
| ClinicalTrials.gov Identifier   | NCT00405886 |
| Health Authority                | Germany: Federal Institute for Drugs and Medical Devices |
## Epidemiology of Hearing Loss in Diabetic and Non-Diabetic Veterans

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<td>Sponsors and collaborators</td>
<td>Department of Veterans Affairs</td>
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<td>Information provided by</td>
<td>Department of Veterans Affairs</td>
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<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT00018486</td>
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<tr>
<td>Purpose</td>
<td>The purpose of this study is to determine if individuals with diabetes are at increased risk of hearing impairment or tinnitus (the perception of ringing or noises in the ears or head). An important goal of this research is also to obtain a better understanding of possible interactions between hearing disorders and other chronic conditions, such as diabetes. Participation in this research will be for a few hours only, to be scheduled at the participant's convenience and according to the testing schedules of the different clinics involved.</td>
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<tr>
<td>Condition(s)</td>
<td>Diabetes</td>
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<td>Tinnitus</td>
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<tr>
<td>Study type and design:</td>
<td>Observational, Screening, Cross-Sectional, Random Sample, Retrospective/Prospective Study</td>
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<td>Official Title</td>
<td>Epidemiology of Hearing Loss in Diabetic and Non-Diabetic Veterans</td>
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<td>Study start</td>
<td>April 1999</td>
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<td>Study completion</td>
<td>March 2004</td>
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<td>Participants (age)</td>
<td>21 Years – 80 Years</td>
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<td>Gender</td>
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<tr>
<td>Eligibility criteria</td>
<td>Any participants over 21 years of age and under 80 who do not have an end-stage disease</td>
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<td>Location</td>
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<td></td>
<td>Portland VA Medical Center, Portland, Oregon, 97201, United States</td>
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<tr>
<td>Study ID Numbers</td>
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<td>Last Updated</td>
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<td>Record first received</td>
<td>July 3, 2001</td>
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## Preventing Chronic Whiplash Pain

<table>
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<tr>
<th>Current status</th>
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<td>Sponsors and collaborators</td>
<td>National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)</td>
</tr>
<tr>
<td>Information provided by</td>
<td>National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)</td>
</tr>
<tr>
<td>ClinicalTrials.gov Identifier</td>
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</table>
### Purpose
This study is aimed at developing ways to prevent acute pain from becoming chronic pain—specifically, pain associated with whiplash-associated disorders (WADs) from motor vehicle accidents. Research on the development of chronic pain due to musculoskeletal injury suggests that a person’s initial emotional reactions, particularly fear of reinjury and subsequent avoidance of activity, contribute significantly to chronic pain and persistent disability. We will treat people with WADs during the first three months after a motor vehicle accident with a behavioral and physical exercise program designed to encourage activity and discourage continued fear of movement, pain, and disability. We will evaluate the effectiveness of two anxiety-reduction treatments compared to standard care in reducing pain and activity limitations in people with WADs in the 2-3 months following motor vehicle accidents.

### Condition(s)
Whiplash Injuries

### Interventions
Behavior: Behavioral treatments  
Behavior: Physical therapy

### Phase
Phase III

### Study type and design:
Interventional, Prevention, Randomized, Single Blind, Active Control, Single Group Assignment, Safety Study

### Official Title
Preventing Chronic Whiplash Pain: Biobehavioral Approach

### Further study details
More than 1.8 million people in the United States suffer from chronic pain and disability following motor vehicle accidents (MVAs) each year. The majority of these cases start with a relatively minor neck injury. The Quebec Task Force Study on Whiplash Associated Disorders (WAD) was created in 1989 to determine the clinical, public health, social, and financial determinants of WAD. Multiple studies have described the clinical features of WAD, which include neck, shoulder, arm, low back, and head pain; tinnitus; visual symptoms; dizziness; temporomandibular joint pain; and paraesthesias. Onset of these symptoms after the injury is usually delayed for several hours and worsens within 24-48 hours. Neck pain is the most frequent symptom, and between 14% and 42% of patients with WAD develop chronic neck pain symptoms. Studies suggest that the neck pain will either resolve in the first few months or persist indefinitely. One variable that may predict outcome after an MVA is the acute emotional response immediately after the MVA.

A severe emotional reaction accompanied by neck pain and stiffness after an MVA could lead an injured person to avoid subsequent physical activity through such mechanisms as fear avoidance and fear of reinjury. Research investigating the evolution of chronic pain due to musculoskeletal injury suggests that initial emotional reactivity, particularly fear of reinjury and subsequent activity avoidance, contributes significantly to unremitting pain and persistent disability. Research based on this model has shown that early interventions targeting normalization of excessive emotionality and restriction of activities associated with fear following injury effectively prevent chronic pain due to back injury. No previous study has sought to intervene during the first three months after an MVA with a behavioral and physical exercise program to encourage activity and discourage continued fear of movement, pain and disability.

This study consists of two primary components: (1) We will evaluate the effectiveness of two anxiety-reduction treatments compared to standard care in reducing pain and activity limitations in patients with WADs 2-3 months following MVAs.
We will test whether psychological responses to the initial trauma such as fear avoidance, fear of injury, and negative affectivity discriminate between symptomatic WAD patients and WAD sufferers whose symptoms had resolved 2-3 months post-MVA.

<table>
<thead>
<tr>
<th>Primary Outcomes</th>
<th>Pain; functional activity; mood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary Outcomes</td>
<td>Fear avoidance; range of motion/strength; physical symptoms</td>
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<tr>
<td>Expected Total Enrollment</td>
<td>300</td>
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<tr>
<td>Study start</td>
<td>May 2001</td>
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<tr>
<td>Study completion</td>
<td>February 2007</td>
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<tr>
<td>Participants (age)</td>
<td>20 Years – 65 Years</td>
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<tr>
<td>Gender</td>
<td>Both</td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>Have whiplash injury following a motor vehicle accident in the prior 4-10 weeks</td>
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<tr>
<td>Location</td>
<td>United States, Washington</td>
</tr>
<tr>
<td>Study chairs or principal investigators</td>
<td>Dennis C. Turk, PhD, Principal Investigator, University of Washington</td>
</tr>
<tr>
<td>Study ID Numbers</td>
<td>R01 AR47298; NIAMS-064</td>
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<td>Record first received</td>
<td>July 16, 2001</td>
</tr>
<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT00021476</td>
</tr>
<tr>
<td>Health Authority</td>
<td>United States: Federal Government</td>
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</tbody>
</table>

**Sildenafil For Meniere's Disease**

<table>
<thead>
<tr>
<th>Current status</th>
<th>completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsors and collaborators</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Information provided by</td>
<td>Pfizer</td>
</tr>
<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT00145483</td>
</tr>
<tr>
<td>Purpose</td>
<td>Meniere's disease affects a person's sense of balance. An attack can last 20 minutes to 2 hours or longer. Symptoms include rotational vertigo, hearing loss, tinnitus and a sensation of fullness in the affected ear and may be associated with nausea and vomiting. One hypothesis is that Meniere's disease is caused by the excessive accumulation of fluid in the balance tubes within the inner ear. Sildenafil may alleviate the symptoms due to its vasodilatory activity. The purpose of this study is to assess the safety and efficacy of sildenafil (Viagra) compared with placebo on symptoms during one acute attack.</td>
</tr>
<tr>
<td>Condition(s)</td>
<td>Meniere's Disease</td>
</tr>
<tr>
<td>Interventions</td>
<td>Drug: Sildenafil</td>
</tr>
<tr>
<td>Phase</td>
<td>Phase II</td>
</tr>
<tr>
<td>Study type and design</td>
<td>Interventional, Treatment, Randomized, Double-Blind, Placebo Control, Parallel Assignment, Safety/Efficacy Study</td>
</tr>
<tr>
<td>----------------------</td>
<td>---------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Official Title</td>
<td>A Multicentre, Double-Blind, Randomized, Placebo-Controlled, Parallel Group Study Of The Efficacy and Safety Of Sildenafil Given For The Acute Treatment Of Meniere's Disease</td>
</tr>
<tr>
<td>Primary Outcomes</td>
<td>Vertigo Response (4 x 6 point scale); Balance (6 point scale)</td>
</tr>
<tr>
<td>Secondary Outcomes</td>
<td>Hearing/Tinnitus; Ear, Nose &amp; Pressure/Fullness; Perf. daily activities; Nausea; Vomiting; Func. Response; Duration of the Attack and Vertigo; Rescue Medications Use; Acceptability to subject; Composite Assessment Score; Comparison to Previous Attack</td>
</tr>
<tr>
<td>Expected Total Enrollment</td>
<td>180</td>
</tr>
<tr>
<td>Study start</td>
<td>June 2002</td>
</tr>
<tr>
<td>Participants (age)</td>
<td>18 Years – 75 Years</td>
</tr>
<tr>
<td>Gender</td>
<td>Both</td>
</tr>
<tr>
<td>Eligibility inclusion criteria</td>
<td>Active Meniere's disease (2 or more definitive spontaneous episodes of vertigo 20 minutes or longer, plus hearing loss on at least 1 occasion, tinnitus or aural fullness) with confirmed diagnosis</td>
</tr>
</tbody>
</table>
| Eligibility exclusion criteria | - Pregnant or breast feeding females or fertile females unwilling to use agreed contraceptive methods  
- severe Meniere's diseased (more than 8 attacks per month)  
- previous ear surgery  
- intratympanic perfusions of steroids or gentamicin; requiring other medications contraindicated for Viagra (eg. nitrates)  
- with medical conditions that make Viagra contraindicated |
| Location             | Australia, New South Wales  
Pfizer Investigational Site, Bondi Junction, New South Wales, Australia  
Australia, Queensland  
Pfizer Investigational Site, BRISBANE, Queensland, Australia  
Australia, Victoria  
Pfizer Investigational Site, East Melbourne, Victoria, Australia  
Pfizer Investigational Site, Melbourne, Victoria, Australia |
| Study chairs or principal investigators | Pfizer CT.gov Call Center, Study Director, Pfizer |
| Study ID Numbers     | A1481107 |
| Last Updated         | November 22, 2006 |
| Record first received | September 1, 2005 |
| ClinicalTrials.gov Identifier | NCT00145483 |
| Health Authority     | Australia: Department of Health and Ageing Therapeutic Goods Administration |
Use-induced reorganisation of the central auditory system in tinnitus

<table>
<thead>
<tr>
<th>Current status</th>
<th>completed</th>
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</thead>
<tbody>
<tr>
<td>ISRCTN Register</td>
<td>ISRCTN80506415</td>
</tr>
</tbody>
</table>

**Hypothesis**
Chronic subjective tinnitus is the perception of a (usually high-frequency) sound in the absence of an objective physical source. Up to now, there is no generally accepted view how these phantom sounds come about, and also no cure. A broadly accepted view states that this symptom is not only reflected but caused by changes in the central nervous system. Based on a recent study (Weisz et al), we argue that tinnitus is related to changes in spontaneous activity patterns, that is an Alpha reduction and Delta enhancement (A/D) over temporal regions.

The enhancement of the A/D ratio, respectively the delta band by means of several neurofeedback training protocols - results in ameliorations of the psychoacoustical (perceived loudness) and psychological (subjective distress) tinnitus variables.

**Condition(s)**
Chronic subjective tinnitus

**Interventions**
In this trial we will investigate how different neurofeedback protocols affect distress variables and psychoacoustic measures. One group has to enhance alpha and reduce delta, the other group will only reduce delta. The neurofeedback training consists of ten sessions over three or four weeks.

**Study type and design**
Randomised controlled trial

**Official title**
Use-induced reorganisation of the central auditory system in tinnitus

**Primary outcomes**
Measured quantity of alpha and delta band frequency ranges (e.g. the alpha/delta ratio, or the delta band only) in the Electroencephalogram (EEG)

**Secondary outcomes**
1. Perceived loudness of the tinnitus (matched to a 1 kHz pure tone)
2. Tinnitus related distress (operationalised with a standard German questionnaire, Goebel et al., 1998)

**Target number of participants**
20

**Study start**
1 June 2004

**Study end**
30 April 2006

**Research ethics review**
No ethics information provided at time of registration

**Eligibility criteria**
Two groups consisting of ten tinnitus sufferers each will be treated with a neurofeedback training. Any tinnitus sufferer can participate with no need to exclude subjects.

**Sponsors details**
German Research Foundation (Deutsche Forschungsgemeinschaft)
Kennedyallee 40, Bonn, 53170, Germany
Phone +49 (0)228 8851
Fax +49 (0)228 8852777
postmaster@dfg.de
Efficacy of hydroxyethyl starch (HES) 130/0.4 vs glucose solution in haemodilution therapy of idiopathic sudden hearing loss: a dose-finding, double-blind multicentre trial

<table>
<thead>
<tr>
<th>Current status</th>
<th>ISRCTN Register</th>
<th>ISRCTN26222607</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsors and collaborators</td>
<td>Fresenius Kabi Deutschland GmbH (Germany)</td>
<td></td>
</tr>
<tr>
<td>Hypothesis</td>
<td>Obtain first data on HES 130/0.4 (hydroxyethyl starch) as monotherapy in patients with acute idiopathic sudden sensorineural hearing loss (ISSNHL).</td>
<td></td>
</tr>
<tr>
<td>Condition(s)</td>
<td>Sudden hearing loss</td>
<td></td>
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<tr>
<td>Interventions</td>
<td>Infusion of 750 ml per day with HES 45 g per day (group H), 30 g per day (M), 15 g per day (L), or glucose 5% (G) acting as ‘placebo’ control over 6 days.</td>
<td></td>
</tr>
<tr>
<td>Study type and design</td>
<td>Randomised controlled trial</td>
<td></td>
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<tr>
<td>Official title</td>
<td>Efficacy of hydroxyethyl starch (HES) 130/0.4 vs glucose solution in haemodilution therapy of idiopathic sudden hearing loss: a dose-finding, double-blind multicentre trial</td>
<td></td>
</tr>
<tr>
<td>Acronym</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Primary Outcomes</td>
<td>Absolute hearing gain (AHG) in decibel at Day 7, calculated as mean audiometric hearing threshold (MAHT) at baseline minus MAHT at Day 7, whereby MAHT was the arithmetic mean of the hearing thresholds in dB at the main speech frequencies of 0.5, 1, 2, 3, and 4 kilohertz</td>
<td></td>
</tr>
<tr>
<td>Secondary Outcomes</td>
<td>Efficacy:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- AHG at other timepoints (i.e. Days 3, 14, and 90)</td>
<td></td>
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<tr>
<td></td>
<td>- Hearing gain based on the Schwab/Ewert formula i.e. the arithmetic mean of the delogarithmmed pure tone thresholds</td>
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<tr>
<td></td>
<td>- AHG based on arithmetic and geometric MAHT calculated only on speech frequencies with an initial hearing loss of 20 dB or more</td>
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<tr>
<td></td>
<td>- Outcome categorised in complete/partial/no recovery or deterioration</td>
<td></td>
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<tr>
<td></td>
<td>- Changes of subjective hearing, vertigo, and tinnitus</td>
<td></td>
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<tr>
<td>Safety:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Adverse events, laboratory parameters (haematology, haemostasis, clinical chemistry, urinalysis), and vital signs</td>
<td></td>
</tr>
</tbody>
</table>
Target number of participants | 210
---|---
Study start | 1 November 2000
Study end | 31 December 2002
Eligibility criteria | 210 inpatients with first-time idiopathic sudden sensorineural hearing loss (ISSNHL) of 20 dB or more at two or more frequencies and 95 dB or less at all of the speech frequencies (0.5, 1.0, 2.0, 3.0, 4.0 kHz) with respect to the other (normal) ear for up to 7 days.

Sponsors details | Fresenius Kabi Deutschland GmbH
Else Kröner Str. 1
Bad Homburg v.d.H
61352
Germany
Phone +49 (0)6172 686 7324
Fax +49 (0)6172 686 8749
Daniela.Baus@fresenius-kabi.com

Contact | Prof Eckart Klemm
HNO-Klinik Krankenhaus Dresden-Friedrichstadt
Friedrichstr. 41
Dresden
01067
Germany
Phone +49 (0)351 480 1220
Fax +49 (0)351 480 1229
Raehder-Co@khdf.de

Local reference numbers | HS-13-26-EU
Date assigned | 09/02/2005
ISRCTN Register | ISRCTN26222607

Source: Auris Medical Cochlear therapies www.aurismedical.com

**AM-101**

**Treatment of inner ear tinnitus**

<table>
<thead>
<tr>
<th>Official Title</th>
<th>AM-101 – Treatment of inner ear tinnitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current status (22 February 2007)</td>
<td>Auris Medical initiated its first clinical trial with AM-101, its investigational drug for the treatment of inner ear tinnitus. The primary objective of the double blind, randomised, placebo-controlled trial with dose escalation is to evaluate the safety of intratympanically delivered AM-101 in patients suffering from tinnitus following acute noise trauma. The secondary objective of the study is a preliminary evaluation of the potential therapeutic benefit of AM-101. Patients whose tinnitus set in less than three months ago and proved to be refractory to a first-line treatment with glucocorticoids will be enrolled in a maximum of 4 dose cohorts. The clinical trial with AM-101 will be performed at the ENT departments of four clinics of the German Bundeswehr (Ulm, Berlin, Hamburg, Koblenz) with Professor Heinz Maier, MD, acting as lead investigator.</td>
</tr>
<tr>
<td>Purpose</td>
<td>A large number of tinnitus cases may be due to single or repeated incidents of excitotoxicity in the cochlea, which can be provoked e.g. by exposure to excessive noise, fluctuations in the blood supply to the cochlea or certain ototoxic medications. Excitotoxicity leads through the excessive release of the neurotransmitter glutamate to neural degeneration, which may in turn lead to tinnitus. While the exact mechanisms responsible for the appearance of tinnitus following excitotoxicity remain to be elucidated, it seems highly likely that some dysregulation of cochlear NMDA receptors lies at the heart of the problem. Accumulating evidence suggests that the “phantom sound” is generated by dysregulated NMDA receptors which produce aberrant firing of the auditory nerve. AM-101 is a non-competitive antagonist of NMDA receptors which has shown to suppress tinnitus in animal models without affecting regular activity of the auditory nerve, i.e. without provoking hearing loss. In 2007, a phase I/II clinical trial with the compound involving 4 clinics of the German Bundeswehr will evaluate the compound’s safety as well as potential first signs of efficacy in humans.</td>
</tr>
<tr>
<td>Important notice</td>
<td>We are currently getting a lot of inquiries about inclusion in clinical trials with AM-101 or regarding the availability of AM-101 as a treatment. We would like to point out that AM-101 like any other drug will be the subject of mandatory clinical trials in accordance with applicable regulations and laws. The clinical evaluation of any drug’s safety and efficacy is a long process, therefore even in the best case AM-101 will not be available to the general public shortly. As for inclusion in a clinical trial with AM-101, patients will be recruited according to well-defined inclusion and exclusion criteria, through appropriate communication means and according to a precise study protocol. Therefore we cannot offer participation in a clinical trial with AM-101 to anyone who is contacting us for this purpose. Thank you for your understanding.</td>
</tr>
</tbody>
</table>

Source: www.northstarneuro.com/clinicaltrials

SAHALE

| Current status | Not currently enrolling |
| Sponsors and collaborators | Northstar has partnered with the Medical College of Wisconsin in Milwaukee WI to complete the SAHALE feasibility study. |
| Purpose | SAHALE is a feasibility study designed to assess the safety and effectiveness of the Renova-TT™ Cortical Stimulation System* in treating patients with severe tinnitus. This is an FDA approved clinical research study. Tinnitus is the sensation of hearing in the absence of external sounds. It can be a relatively benign sound that is heard only occasionally, or it can be a devastating roar 24 hours a day accompanied by hyperacusis (sounds are perceived as very loud) and sound distortion. Varying degrees of subjective tinnitus occur between these extremes. The more severe end of this spectrum can be extremely debilitating, interfering with concentration and sleep. |
| Participants | The patients included in this study have suffered from subjective unilateral or bilateral tinnitus for more than one year. Patients are screened, imaged, and evaluated in order to enroll patients appropriate for stimulation system implant. |
| Contact | Allen Wyler 206 902-1966 awyler@northstarneuro.com |
LidoPAIN® TV

<table>
<thead>
<tr>
<th>Description</th>
<th>LidoPAIN® TV is a topical lidocaine patch applied to the periauricular skin region (behind the ear) for the treatment of tinnitus. This product releases doses of lidocaine into nerve endings located behind the ear. Tinnitus is characterized by a constant or intermittent hissing, buzzing or ringing noise in the ear that affects over 50 million Americans. There are many causes of tinnitus, including defects in nerve conduction and one of the side effects of some medications; however, there are no currently approved treatments.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage of Development</td>
<td>While an IND application for LidoPAIN TV has not been submitted to the FDA, a foreign IND equivalent was filed by EpiCept in Europe in June 2001. A European Phase II clinical trial in subjects with tinnitus was completed in 2002. Subjects utilizing the LidoPAIN TV patch perceived a beneficial effect as compared to subjects given the placebo patch.</td>
</tr>
<tr>
<td>For more information see</td>
<td><a href="http://www.epicept.com/Product_Pipeline/Pain/">www.epicept.com/Product_Pipeline/Pain/</a></td>
</tr>
</tbody>
</table>