

**Tinnitus and quality of life -
Validation of the Tinnitus Handicap Inventory and Use of
Acoustic CR[®]-neuromodulation Treatment in Patients with
Chronic Subjective Tinnitus**

PhD theses

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INTRODUCTION

The term 'ringing in the ears' (also called 'tinnitus') comes from the Latin word 'tinnire', which means 'ringing'. Tinnitus is actually a *subjective* symptom; a sound that is perceived only by the patient without any corresponding external acoustic stimulus and cannot be heard by an observer. *Objective* tinnitus is not so common; this type of tinnitus can be perceived by an observer using e.g. a phonendoscope or other acoustic devices.

In our society, tinnitus has a growing significance: surveys show that 10 to 19% of the population may be affected and the condition requires very complex and complicated diagnostic methods, with unrevealed cause in many cases. Research studies of the last two decades provided many different theories for the etiology and pathogenesis of tinnitus but the entire mechanism is still unclear. Nevertheless, it is widely recognized that central brain structures play a dominant role in the genesis of tinnitus, making researchers focus on the central nervous system.

Almost everyone has experienced tinnitus episodes in his/her lifetime for some seconds. While this type of tinnitus does not represent a disturbing factor, long-lasting, monotonous, uninterrupted tinnitus episodes (even those lasting for some hours or days) certainly have a negative impact on our daily routine and quality of life (QOL). In almost all cases it is associated with a psychic burden, the extent of which depends on how the patient relates to his/her symptoms, what high his/her stress tolerance is and what kind of psychic coping strategies he/she uses.

Research study results published in the last few years also explain why does long-lasting tinnitus provoke negative emotions and growing psychic pain in the affected person: the essential role of the limbic system (emotional centre) has been demonstrated in the pathogenesis of tinnitus – in addition to that of the auditory pathway and other cerebral regions. Psychic symptoms may be accompanied by additional somatic symptoms such as headache, pain in the muscles of the neck, nape and shoulder,

sweating, dizziness, etc. According to Jastreboff P.J.'s neurophysiologic model, these are caused by altered responsiveness of the autonomic nervous system, several changes in rational reactions and cognitive processes. The above factors reinforce negative perception of tinnitus and associated negative reactions, leading to the so-called self-generating „tinnitus-spiral”, also considered as a vicious circle.

Majority of related studies show a positive correlation between tinnitus and the onset of anxiety disorders and depression, suggesting a common etiology. The factors determining the severity of tinnitus include the presence of depression and anxiety disorders, the severity of hearing loss, as well as the frequency, loudness and duration of tinnitus but even gender, age and education level may have an important role. In this respect, study results are not homogenous, sometimes are even contradicting.

Frequency (Hz) and loudness (dB HL) of tinnitus can be measured by pure-tone subjective audiometry and tinnitometry. To evaluate how tinnitus interferes with one's daily life, mainly self-reporting questionnaires should be used. The purpose of these tools is to assess the annoyance and QOL-worsening effects of tinnitus, the extent of the affective disorder, cognitive reactions, or even general problem-solving skills of the patients, which may show large inter-individual variations. The use of such questionnaires allows the therapist or the clinician to have a better understanding of the problem, as well as to elaborate and monitor individualized therapies.

Tinnitus Handicap Inventory is one of the most commonly used self-reporting questionnaire for the assessment of tinnitus patients, the content of which can be adapted to the way of life of the average Hungarian population. It has been translated and validated into many languages, including Danish, Spanish, Korean, Portuguese/Brazilian, Turkish, Italian, Chinese/Cantonese, Singaporean, French, Persian, Hebrew and Chinese/Mandarin adaptations. Consisting of 25 questions,

the questionnaire is divided into functional, emotional and catastrophizing subscales. There are three possible answers for every question: *yes*: 4 points, *sometimes*: 2 points, *no*: 0 point. Total score ranges between 0 and 100. Depending on the latter, the result may be ranked as *insignificant* (0 to 16 points), *mild* (18 to 36 points), *moderate* (38 to 56 points), *severe* (58 to 76 points) and *profound* (78 to 100 points).

So far no validated, reliable tinnitus questionnaire has been constructed in Hungarian – absence of this can be felt both in everyday clinical practice and international research studies.

There is a wide range of tinnitus treatment methods. These procedures and their efficiency show large variations; they are based on different theoretical backgrounds and should be individualized in the most cases.

Acoustic CR[®]-neuromodulation – a patented neurotechnological procedure – provides a novel therapeutic method in chronic subjective tinnitus and has been developed as a result of a more than 10-year research work led by Prof. Dr. Peter Tass. This therapy is based on the following, well-established principle: tinnitus is related to the overactivity of auditory nerve cells arising from a pathologically altered synaptic connectivity between the auditory pathway, auditory cortex and other brain areas. These pathological patterns are then learned and sustained by the brain, due to its plasticity. During acoustic CR[®]-neuromodulation therapy, specific brain areas responsible for the generation of the pathologic sounds are treated directly through the ear by the help of a programmed sound generator/stimulator. The device uses targeted acoustic pulses specifically matched to the patient's individual 'tinnitus profile' so as to gradually attenuate pathologic synchronization and hyperactivity of the neuronal network and reestablish its normal 'desynchrone' working. Meanwhile, the brain 'unlearns' the tinnitus sound – and substitute it with a new functional pattern. Spatial and temporal coordination of this series of tones is ensured by the use of a specific, complex mathematical algorithm.

Acoustic CR[®]-neuromodulation treatment is indicated in mono- or bilateral, *subjective tinnitus* with one specific frequency (socalled *tonal tinnitus*) ranging between 200 and 10000 Hz and a duration of at least 6 months.

In my dissertation, results of two clinical trials are summarized. Subjects of these trials confirmed their intention for participation by signing a patient informed consent form after receiving detailed information on the objectives and process of the clinical trial. The clinical studies were previously approved by the Research Ethics Committee of Semmelweis University (9/2013).

Validation of Tinnitus Handicap Inventory into Hungarian language

OBJECTIVES

The purpose of my study was to adapt Tinnitus Handicap Inventory (THI-US) into Hungarian language (THI-HUN). The former is the original, English tinnitus questionnaire that is one of the most commonly used tool in related international studies and consists of 25 questions. Objectives of the validation process were:

1. To translate THI into Hungarian; Hungarian interpretation and precise wording of the test items.
2. To demonstrate the reliability of the THI-HUN, using the following methods and statistical analyses:
 - Comparison of item-total correlation of THI-US and that of THI-HUN,
 - Measurement of the internal consistency (Cronbach alfa) of THI-HUN questionnaire, comparing it with that of the original English version,

- Testing the correlation between THI-HUN and other questionnaires (4-item Perceived Stress Questionnaire; 9-item, short form Beck Depression Inventory, Visual Analogue Scale),
 - Testing the correlation between THI-HUN and category variables (gender, education level) / continuous variables (age, hearing impairment, duration of tinnitus),
 - Retesting of THI-HUN 2 weeks after the first completion of the questionnaire and identification test-retest correlation; and
 - Factor analysis of THI-HUN.
3. Wording of and giving a Hungarian title to the final, reliable Hungarian version of the questionnaire resulted by the validation process.

SUBJECTS AND METHODS

The study involved 72 subjects with chronic idiopathic subjective tinnitus (43 women and 29 men) who were examined at the Outpatients' Department of Otoneurology, Semmelweis University, Department of Otorhinolaryngology and Head and Neck Surgery. Inclusion criteria were the following: age over 18 years; mono- or bilateral, uninterrupted tinnitus as the main symptom lasting for at least 3 months before study enrollment. Patients with severe psychiatric conditions, non imputable persons and patients not understanding or speaking Hungarian were excluded from the analysis.

First I asked the author of the THI-US, C.W. Newman to give his consent for the translation of THI into Hungarian and test validation. Then 3 independent investigators speaking both languages excellently translated the English text into Hungarian. These 3 translations were then

summarized and integrated in a single document on an audiological and linguistic basis. This document was retranslated into English by a native speaker who was not aware of the original English wording. Following this procedure, the original THI-US and THI results retranslated into English were compared and interpreted by the help of a professional English-speaking investigator. Hungarian adaptation of Tinnitus Handicap Inventory was given the title „Fülzúgás Terheltség Skála” (THI-HUN).

To make a Hungarian adaptation, I intended to compare THI with questionnaires already validated into Hungarian that are being used in practice and – pursuant to the scientific results - may have a correlation with THI-HUN.

At the first visit, after medical check-up, subjects meeting the inclusion criteria were asked about their medical history and underwent a comprehensive ENT examination, pure-tone threshold audiometry (air and bone conduction), tinnitometry and tympanometry.

In addition to THI-HUN, study subjects were asked to complete the following questionnaires: short, 9-item version of Beck's Depression Inventory (BDI); 4-item version of Perceived Stress Scale (PSS4) and 3 subscales – loudness, annoyance and pitch of tinnitus – of Visual Analogue Scale (VAS) in a self-reporting form, under calm conditions.

Two weeks after the first completion of THI-HUN study subjects completed the THI-HUN test repeatedly (test-retest stability), without receiving any new treatment after the first completion of the test or being aware of the previous test results. Recompleted questionnaires were sent to me by post.

STATISTICAL ANALYSIS

- For statistical calculations SPSS 20.0 program package was used.
- Correlation between the total set of item and individual items of Hungarian THI was tested by the help of item-total correlation.
- To measure the internal reliability, Cronbach alfa was applied.

- Connections between measuring tools, continuous variables and THI, as well as test-retest correlation were examined using the Pearson's correlation coefficient.
- To test the correlation with gender and other category variables, independent t-test and analysis of variance (ANOVA) methods were applied, respectively.
- Factor analysis was applied to demonstrate the validity of the constructed subscales.

RESULTS, CONCLUSIONS

Average duration of tinnitus in the 72 subjects with chronic idiopathic tinnitus was 4.16 years (SD: 5.19, min.: 0.25, max.: 35 years). Their mean age was 49.86 years (SD: 14.34, min.: 20, max.: 79 years). 35 patients had a monolateral tinnitus (13 on the right and 22 on the left side), while 37 patients experienced tinnitus in both ears or in the head. Distribution of education level was the following: 29 patients had a college/university degree, 42 had a high-school diploma and 1 subject had a primary school degree.

Every patient had a normal otoscopic finding with a normal middle ear pressure confirmed by tympanometry. Air conduction threshold was considered as the extent of hearing impairment; no ABG between air and bone conduction was recorded.

Considering the mean values of air conduction thresholds measured at 125, 250, 500, 1000, 2000, 4000, 8000 Hz in pure-tone threshold audiometry, we have found the following. On the right ear: normal hearing capacity or slight hearing impairment in 51 subjects (71%); mild, moderate and severe hearing impairment was measured in 15 (21%), 5 (7%) and 1 patients (1%), respectively. Left ear: normal hearing or slight hearing impairment in 53 subjects (74%); mild, moderate and severe hearing loss in 11 (15%), 7 (10%) and 1 patient, respectively. No profound hypacusis was recorded.

With tinnitometry, mean/SD of tinnitus frequency on 53 ears was 3329±2775 Hz; that of tinnitus loudness was 39.9±19.43 dB HL. Measurement of tinnitus was unsuccessful on 19 ears.

Statistical analysis of methods applied in the validation process of THI-HUN provided the following results:

- Internal reliability of THI-HUN is excellent with a Cronbach alfa value of 0.95.
- Item-total correlation coefficient range of THI-HUN is appropriate (r=0.3 to 0.8); its minimum and maximum limit values are both higher than those of the original English version (r=0.22-0.77).
- THI-HUN showed a significant correlation with the measuring tools tested in this study – 4-item Perceived Stress Scale, 9-item short Beck Depression Inventory and Visual Analogue Scale tinnitus loudness and annoyance subscales –; no correlation with VAS pitch of tinnitus was found.
- Gender, age and education level of patients did not seem to have any effect on the result of THI-HUN.
- Degree of hearing loss and duration of tinnitus have a detrimental effect on THI-HUN score.
- Tinnitometry-confirmed loudness of tinnitus showed a correlation with the outcome of THI-HUN test, while no relationship with the frequency of tinnitus was detected.
- Test-retest correlation of THI-HUN is high: r=0.97.

- Using factor analysis, I have not succeeded to put the items of THI-HUN into the subscales structures defined in the original Tinnitus Handicap Inventory.

Being the first Hungarian questionnaire for tinnitus assessment, THI-HUN makes up a deficiency. As demonstrated by the results of my study, it helps assess the detrimental impact of tinnitus on the daily life of the affected person, and evaluate the extent of tinnitus-provoked distress. Consequently, it is an appropriate tool for the documentation and monitoring the quality of life of tinnitus patients. It can be widely and simply used both in everyday clinical practice and scientific clinical trials; thereby it is suitable for comparative analyses of international research studies.

Acoustic CR[®]-neuromodulation treatment

OBJECTIVES

Acoustic CR[®]-neuromodulation is a new treatment method in chronic subjective tinnitus patients. Hungary was one of the first European countries where it has become available. Purposes of my study were:

1. To use acoustic CR[®]-neuromodulation therapy first in Hungary, in a group of patients with chronic subjective tinnitus who were previously examined according to the protocol.
2. To evaluate and process clinical outcomes and results collected during the first 6 months of acoustic CR[®]-neuromodulation treatment in 27 patients.
3. To monitor the changes in tinnitus perception during acoustic CR[®]-neuromodulation therapy, using the Hungarian version of THI (THI-HUN) and Visual Analogue Scale (loudness, annoyance

and pitch of tinnitus), as well as the changes in loudness (dB HL) and pitch (Hz) of tinnitus by the help of tinnitometry.

4. In line with the first clinical study of P. Tass et al. and pursuant to the hypothesis, to demonstrate or reject the therapy-induced, reduction of the pitch and/or loudness of tinnitus, as well as improvement in scores of the applied symptom-evaluating tests – THI and VAS (loudness, annoyance and pitch of tinnitus).

SUBJECTS AND METHODS

Twenty-seven patients suffering from chronic subjective tinnitus were treated with acoustic CR[®]-neuromodulation on an outpatient basis. Prior to treatment initiation, each subject underwent a comprehensive examination pursuant to the protocol recommended by the Hungarian College of ENT specialists, in order to identify subjects eligible for therapy.

To ensure the applicability of acoustic CR[®]-neuromodulation treatment and promote therapeutic success, the following inclusion criteria were set: chronic subjective tinnitus with a duration of longer than 6 months; age over 18 years; mono- or bilateral, mono- or multifrequency, tonal subjective tinnitus between 200 and 10000 Hz with a measurable frequency; a sufficient hearing threshold around the treated frequency range so that the patient can hear the therapeutic sounds - max.50 dB HL hearing impairment between 125 and 12000 Hz -; and the absence of other ongoing tinnitus therapies. Exclusion criteria: objective tinnitus, Ménière's disease, psychiatric disease, acoustic hallucinations, tinnitus related to a temporomandibular arthropathy, brainstem disorders.

Before starting acoustic CR[®]-neuromodulation therapy, a general ENT examination (mainly otoscopic finding), pure-tone threshold audiometry (measuring frequencies: 125, 250, 500, 1000, 2000, 4000, 6000, 8000, 12000 Hz), tinnitometry and tympanometry were carried out.

A specific software and hardware unit were used for the setting and recording of acoustic CR®-neuromodulation therapeutic sounds; meanwhile, pitch (Hz) and loudness (dB HL) of tinnitus of the patients were measured repeatedly. The above software allows us to measure tinnitus frequency and loudness in 1 Hz and 1 dB steps, in a range of 0 to 13000 Hz, and 0-90 dB HL, respectively. Measurement and setting were performed in a silent room, through open ear tips.

Once tinnitus profile has been determined, the software is generating 4 stimulation sounds matched to the detected pitch and loudness of tinnitus. Prior to recording them on acoustic CR®-neuromodulation stimulator, therapeutic sounds were tested by the patient for about 30 minutes to exclude any potential annoyance. During the course of treatment, the patient listened to the stimulation sounds for approximately 4 to 6 hours a day (at least 2 hours without interruptions), while being awake and performing his/her daily routine. These stimulation sounds were previously recorded on the stimulator through an open ear tip connected to the equipment.

Check-ups were carried out in week 2, 4, 8 and 12, then as required by the patient but at least in every 4 to 6 weeks. At these control visits, the pitch and loudness of tinnitus were measured repeatedly, with a readjustment of stimulation sounds in case of detected changes. In order to monitor the changes in tinnitus, subjects were asked to complete a THI-HUN and a VAS measuring the loudness, annoyance and pitch of tinnitus at each control visit.

Being the software for acoustic CR®-neuromodulation patented, stimulation tones are generated by the software during the initiation of the neuromodulation process. Thus, no stimulation tones other than those created by the software can be set. Consequently, it was not possible to create a placebo group to be treated with therapeutic tones of different frequency not generated by the mathematical software. For all patients,

their pre-neuromodulated, chronic subjective tinnitus resistant to other therapies was considered as self-controlled baseline.

STATISTICAL ANALYSIS

During the 6-month therapy, a linear mixed model was used for the statistical analysis of differences between the examined variables. Dependent variables included tinnitus frequency (Hz), tinnitus loudness (dB HL), VAS loudness (%), VAS annoyance (%) and VAS pitch of tinnitus (%). The explaining variables integrated into the models were: indication of measurement and the measured side; gender; age categories (0 to 40 years, 41 to 60 years, >60 years); hearing loss severity and tinnitus duration. Linear mixed model was matched with the so-called Restricted Maximum Likelihood method.

Difference between the values measured at the baseline and after 6 months of treatment, as well as significance of other potential explaining variables were analyzed with F-test, at a significance level of 0.05 (5%). Ignoring non-significant variables, the model was readapted and used for the determination of the estimated change, standard deviation and 95% CI of the estimations. The analyses were performed by the help of R 3.02. statistical program and the so-called nlme package.

RESULTS, CONCLUSIONS

Outcomes of the first 6-month acoustic CR®-neuromodulation treatment of 27 patients with chronic subjective tinnitus were analyzed.

Four, 6 and 17 subjects had a right-sided, a left-sided and a bilateral tinnitus, respectively. Each subject with unilateral tinnitus had a single-frequency tinnitus; of the patients with bilateral tinnitus, 10 subjects experienced the same tinnitus frequency in both ears, while 7 patients reported two different tinnitus frequencies in the right and left ear. In the latter group, difference of the two perceived frequency exceeded 200 Hz in all cases.

During the 6-month treatment period, significant adverse event had been detected only in one subject treated with bilateral tinnitus who reported a sudden increase of the loudness of tinnitus in the right ear. This event required the discontinuation of therapy on the right side. All the other subjects were treated without adverse effects.

With pure-tone threshold audiometry, we have found normal hearing capacity in one case, sensorineural hearing loss on the others on the affected side. Based on mean air conduction values in the ears with hearing impairment, 37, 3, 2 and 1 patients had slight, mild, moderate and severe hearing loss, respectively. During the 6-month treatment period, no changes in the results of pure-tone audiometry were detected. Tympanometry showed normal middle ear pressure in all cases, with normal otoscopic findings.

Tinnitometry results measured with acoustic CR®-neuromodulation software, mean frequency of tinnitus was 5037±3093 Hz and 5540±3015 Hz, mean loudness of tinnitus was 49±20 dB HL and 43±20 dB HL on the right (21 ears) and on the left ears (23 ears), respectively.

1. Summarizing the results of clinical application of acoustic CR®-neuromodulation and the outcomes of the 6-month therapy, the following conclusions have been made:

- Based on the statistical analysis of tinnitometry results of a 6-month treatment in 27 subjects with chronic subjective tinnitus, a significant improvement (reduction) of the pitch and loudness of tinnitus was demonstrated.
- Due to the lack of control group, the efficacy of acoustic CR®-neuromodulation therapy cannot be evaluated but the results of Tinnitus Handicap Inventory and Visual Analogue Scale

(tinnitus annoyance and pitch of tinnitus) showed a reduction of complaints during the 6-month study period. Nevertheless, no significant improvement of Visual Analogue Scale (tinnitus loudness) scores were detected. These results are partly consistent with those observed in the first clinical study by P. Tass et al.

2. In Hungary, my study was the first to evaluate the findings gained during the use of acoustic CR®-neuromodulation in clinical practice and to analyze and summarize the output data of the therapeutic outcomes. Relevance of my study lies in the fact that therapy of subjective tinnitus is still a challenging problem. Consequently, any new therapeutic method or procedure may represent a promising and beneficial option for the patients.
3. In this study, in which I have performed acoustic CR®-neuromodulation therapy on a small sample size, results seem to be promising but additional data and further controlled clinical trials with larger sample size will be required to demonstrate the efficacy of the therapy.

DISSERTATION-RELATED PUBLICATIONS

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