A central nervous system approach to tinnitus

Carlijn Emily Louise Hoekstra

A central nervous system approach to tinnitus

Tinnitus vanuit het centraal zenuwstelsel bekeken
(met een samenvatting in het Nederlands)

Proefschrift

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General Introduction and Outline of the Thesis

Ebers papyrus

GENERAL INTRODUCTION

History

The word tinnitus is derived from the Latin word tinnire, meaning “to ring” or “a ringing”. Descriptions of tinnitus are found throughout history. The oldest recordings are in the Ebers papyrus from ancient Egypt (16th century BC), which describes a treatment for a “bewitched ear” (Stephens 1984). Other ancient recordings are found on Assyrian clay tablets (7th century BC) and in Greek, Roman and Islamic texts (Stephens 1984).

Definition tinnitus

Tinnitus is a diverse symptom with many different manifestations. To specify this sensation better different classifications and/or definitions for tinnitus have been proposed over the years focused on pathophysiology, location or severity. However, none has universally been accepted. Table 1 shows an overview of the different classification and/or definitions used.

Tinnitus and somatosounds are both perceptions of a sound without an external acoustic stimulus. In the case of somatosounds though, there is an internal somatic acoustic origin of the perceived sound through vascular, muscular or respiratory activity or from the temporomandibular joint (Fortune et al 1999; Henry et al. 2005a; Jastreboff and Jastreboff 2003; Noel and Meyerhoff 2003). This internal sound evokes normal vibratory activity of the basilar membrane in the cochlea, whereas in tinnitus there is an underlying neurophysiological process without any corresponding auditory/vibratory activity in the cochlea. Other used differentiations as objective versus subjective tinnitus and pulsatile versus non-pulsatile tinnitus also aim to differentiate between these two syndromes. We believe these terms to be less adequate because they differentiate on the basis of clinical traits rather than on pathophysiology. Also, the division between objective and subjective tinnitus is error prone because it is possible that a sound that is generated inside the body is not objectified by an examiner, depending on the loudness of the sound and on the skills of the examiner. The division between pulsatile and non-pulsatile tinnitus can be useful to assess the possibility of a somatosound, which are more often pulsatile. Tinnitus on the other hand can sometimes be experienced in a pulsatile manner as well and therefore it is not advisable to use these terms as a definition/classification to differentiate between tinnitus and somatosounds.

Auditory hallucinations and tinnitus are both phantom auditory perceptions of sound. Whereas tinnitus is a *meaningless* sound, auditory hallucinations are *meaningful* sounds (e.g. speech, music), and the two syndromes should be differentiated as such. The differences and similarities between tinnitus, somatosounds and auditory hallucinations are shown graphically in Figure 1.

Table 1 Classifications or definitions used in relation to tinnitus

Classification	Explanation
Normal tinnitus[1]	<5 minutes and <1/week, experienced by most people without hearing loss
Pathological tinnitus[1]	>5 minutes and <1/week, usually by people having hearing loss - acceptable (not bothersome) - unacceptable (disturbing to patient) - temporary (short term) - permanent (constant or intermittent)
Central tinnitus[2]	arises from temporal lobe, auditory nerve, brain stem
Peripheral tinnitus[2]	arises from external auditory canal, middle ear, cochlea
Conduction tinnitus[3]	arises from vibrations in the middle ear
Sensorineural[3] tinnitus	arises from the hair cells or the auditory nerve
Centralized tinnitus[3]	arises from the brain or the central nervous system
Severity 1[4]	type I: mild tinnitus, incidental to another problem type II: moderate-severe tinnitus as primary complaint type III: intractable moderate-severe tinnitus as primary complaint
Severity 2[5]	grade I: audible only in silent environments grade II: audible only in ordinary acoustic environments, masked by loud environmental sounds; can disturb falling asleep, but not sleep in general grade III: audible in all acoustic environments, disturbs falling asleep, can disturb sleep in general, is a dominating problem that affects quality of life
Objective tinnitus[6]	can be heard by the patient as well as the examiner also called extrinsic tinnitus, vibratory tinnitus or pseudotinnitus
Subjective tinnitus[6]	can only be heard by the patient also called tinnitus aurium, or non-auditory tinnitus
Non-auditory tinnitus[7]	projection of the response to stimulation of a sensory system, other than the auditory system, to the auditory system
Pulsatile tinnitus[8]	increased blood flow or lumen stenosis of vascular structures within the cranial cavity, head & neck region, and thoracic cavity lead to turbulence in the blood flow and thus vibrations that reach the cochlea
Somatosounds[9]	generated somatically through a vascular, muscular, respiratory or temporomandibular joint origin

1) Davis and Rafaie 2000, 2) Zenner et al. 2006, 3) Noell and Meyerhoff 2003, 4) Doyle et al. 1987; Heller 2003, 5) Klockhoff and Lindblom 1967, 6) Crummer and Hassan 2004; Fortune et al. 1999; Heller 2003; Henry et al. 2005a; Lockwood et al. 2002; Noell and Meyerhoff 2003; Shulman 1981, 7) Shulman and Goldstein 1984, 8) Fortune et al. 1999; Sismanis 2003, 9) Noell and Meyerhoff 2003; Henry et al. 2005a; Fortune et al. 1999; Jastreboff and Jastreboff 2003

In this thesis, tinnitus is defined as a phantom auditory perception of meaningless sound in the absence of an external or internal acoustic stimulus.

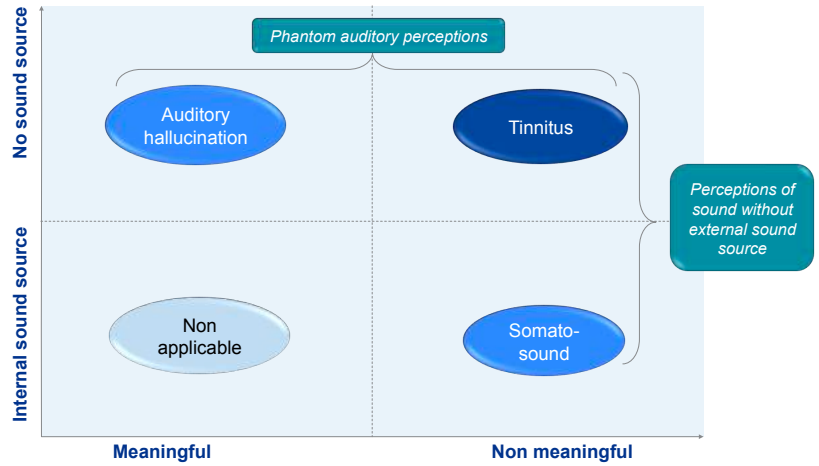

Figure 1 Tinnitus, somatosounds and auditory hallucinations

Prevalence

Tinnitus is a common symptom. It has a prevalence of 7 – 19% in the adult population, according to several epidemiological studies (Axelsson and Ringdahl 1989; Chung et al. 1984; Coles 1984a; Davis 1989a; Nondahl et al. 2002). These percentages differ substantially because these studies were conducted in various countries using different age groups and various definitions and criteria for tinnitus. When the criteria used for tinnitus are broad (including occasional tinnitus), prevalence rates of up to 35% are mentioned (Coles 1984a). The prevalence of tinnitus increases with advancing age and seems to attain a plateau or decrease again after around 60 – 80 years (Chung et al. 1984; Coles 1984b; Davis and Rafaie 2000; Heller 2003; Henry et al. 2005a). Tinnitus can occur in children as well (Baguley and McFerran 1999; Heller 2003). There does not seem to be a strong sexual predisposure. Most studies do not show a difference, but both a male and a female preference have been described (Axelsson and Ringdahl 1989; Coles 1984b; Davis and Rafaie 2000; Heller 2003; Lockwood et al. 2002). Within the group of treatment seeking patients though, there seem to be twice as many men as women (Henry et al. 2005a).

Burden

The greater part of the symptomatic population does not experience the tinnitus as problematic, but in up to 5% of the adult population it does lead to annoyance or it even interferes with the ability to lead a normal life and in 1 – 2% it affects daily life severely (Coles 1984a; Davis 1989; Nondahl et al. 2002). It has been postulated that the intrusiveness of tinnitus can be triggered by emotional stress, psychological factors, bereavement, unemployment, or various physical or mental illnesses (Henry et al. 2005a). Sleep problems are one of the most common additional complaints of tinnitus patients and are reported by about half of those individuals who complain of tinnitus (Henry et al. 2005a; Tyler and Baker 1983). Other often mentioned problems that patients relate to their tinnitus are problems in noisy/social situations (14 – 15%), problems in quiet situations (11%), family problems (7%) or problems at work (4%) (Tyler and Baker 1983). Many patients with tinnitus exhibit signs of psychological disorders, such as depression (28 – 60%) and anxiety (15 – 45%) (Dobie 2003; Folmer et al. 1999; Sullivan et al. 1988; Zoger et al. 2006)..

Characteristics

The characteristics of the perceived tinnitus sound (e.g. description, number of different sounds heard, pitch, onset, presence and location of the sound) can vary enormously between patients. Most patients (75-79%) describe the sound as a tone (ringing, whistling), to others it seems more like a noise (roaring, hissing) (Eggermont 2003; Vernon and Meikle 2003).

Most tinnitus sounds are high pitched. It has been shown that the majority of patients match their tinnitus pitch with a sound frequency above 4000 Hz, with a median pitch at 6000-7000 Hz (Vernon and Meikle 2003; Stouffer and Tyler 1990). In some cases the frequency of the tinnitus may indicate a cause for the tinnitus. Menière's disease has been described to have a characteristic low-pitched roaring tinnitus while noise-induced hearing loss is said to have a high-frequency tinnitus (Perry and Gantz 2000; Schwaber 2003).

Patients experience tinnitus at different loudness levels. Most patients define their tinnitus as loud, even though hearing tests show that the tinnitus occurs at intensities rather close to their hearing threshold at that frequency (<9 dB Sensation Level) (Vernon and Meikle 2003).

Tinnitus can exist of one or multiple sounds. It can be heard in one ear, in both ears or in the head. In this thesis unilateral tinnitus is defined as tinnitus (one or more sounds) perceived in one ear only. Bilateral tinnitus is defined as hearing the same tinnitus sound in both ears. When a different sound is heard in each ear, this is defined as twice unilateral tinnitus. When patients hear multiple sounds, combinations of these descriptions can be used simultaneously.

A number of patients can modulate their tinnitus. Sixty-five to sixty-eight percent of patients have been described to be able to modulate their tinnitus through voluntary muscle contractions of predominantly the head and neck muscles (Levine 1999; Sanchez et al. 2002). It is hypothesized that the existing neural connections between the auditory and the somatosensory system lead to this modulation (Sanchez et al. 2002). Patients who can modulate their tinnitus by jaw movements have been described as well (Pinchoff et al. 1998). Gaze-evoked tinnitus has specifically been described after cerebellopontine angle surgery (Coad et al. 2001).

Pathophysiology

Chronic tinnitus is commonly thought to be a perception, based on activity generated in the brain as a result of functional reorganization of the central auditory system, following damage to the peripheral auditory system (Eggermont and Roberts 2004). This functional reorganization includes alteration of the tonotopic brain maps. This tonotopic reorganization has indeed been shown in humans with tinnitus (Muhlnickel et al. 1998). On the neuronal level, it is thought that this functional reorganization further includes an increased spontaneous firing rate of neurons in the auditory cortex and auditory brainstem, and/or an increased synchronization of spontaneous activity of cortical neurons (Eggermont and Roberts 2004; Norena et al. 1999; Ochi and Eggermont 1997; Roberts et al 2010). This increased synchronous activity hypothesis is supported by results found in magneto-encephalography studies (Schlee et al. 2009; Weisz et al. 2005). This increase in firing rate and synchronization would lead to hyperactivity in the central auditory system. Neuroimaging studies support the notion that tinnitus corresponds to neural hyperactivity. Even though there are many differences across studies, a general trend can be seen that neural activity is enhanced across several centers of the central auditory system (Lanting et al. 2009). Also association of non-auditory areas such as the frontal areas, the limbic system and the cerebellum are found in neuroimaging studies (Lanting et al. 2009; Leaver et al. 2011). The mechanism underlying this increase in spontaneous firing rate and synchronization is thought to be reduced inhibition, which is the consequence of the decreased output from damaged cochlear regions (Eggermont and Roberts 2004; Roberts et al. 2010; Salvi et al. 2000).

Diagnosis

As described above, tinnitus results from damage to the peripheral auditory system. Therefore, tinnitus is usually related to hearing loss. However, the damage to the peripheral auditory system does not have to be to such an extent that a hearing loss can be measured with clinically used diagnostic audiometry. Normal hearing is found in approximately 8 – 18% of patients (Davis and Rafaie 2000; Stouffer and Tyler 1990). The etiology of this damage

to the peripheral auditory system and the subsequent probable hearing loss should be diagnosed. This makes history-taking aimed at potential causes of hearing loss (e.g. duration, onset, family history, possible trauma due to noise overexposure or medication use) and audiometry the most important diagnostic tools in tinnitus. Because many possible causes for hearing loss exist and similar symptoms as somatosounds need to be excluded, the sequence of possible diagnostic steps in tinnitus diagnostics can be virtually endless.

Many recommendations have been made on these diagnostic options (Crummer and Hassan 2004; Fortune et al. 1999; Henry et al. 2005b; Lockwood et al. 2002; Noel and Meyerhoff 2003; Peifer et al. 1999; Perry and Gantz 2000; Schleuning 1991; van de Heyning et al. 2007). To structure the possible examinations in tinnitus diagnosis, the Tinnitus Research Initiative (www.tinnitusresearch.org) has produced a very comprehensive list of potential tests in tinnitus including an elaborate flowchart. In addition, this flowchart refers to literature on these tests. Possible tests that are described include audiometry, audiometric tinnitus analysis, Auditory Brainstem Responses, Oto-acoustic emissions, blood tests, Magnetic Resonance Imaging, Computer Tomography, angiography, echo-doppler, electroencephalography and lumbar puncture.

A drawback of the numerous possible tests in tinnitus is their potentially low yield and the high costs that they could lead to. For virtually none of the possible diagnostic tests, information is available about their added value or cost-effectiveness.

Treatment

Although some therapies may be beneficial for some patients in reducing tinnitus, there is no curative therapy. The role of pharmacotherapy in the treatment of tinnitus is still inconclusive. In 1978 it was shown that intravenous lignocaine may suppress tinnitus temporarily in some patients during 10 – 30 minutes (Melding 1978). Since then a wide range of drugs have been proposed for the treatment of tinnitus but none have proven to be effective in the long run (Dobie 1999; Robinson 2007).

Patients, who also have a significant hearing impairment, may benefit from a hearing aid (Del Bo and Ambrosetti 2007). Not only will this ameliorate their hearing disability, but it can also diminish their tinnitus sensation through masking effects of the amplified surrounding sounds. Masking devices, which stimulate the ear with a sound to mask the tinnitus, might be beneficial to some patients (Hobson et al. 2012). Psychological therapies (e.g. counseling, cognitive behavioral therapy and tinnitus retraining therapy) may diminish tinnitus by lessening the distress caused by it or by improving quality of life by teaching coping strategies, relaxation techniques and distraction skills (Andersson and Lyttkens 1999; Cima et al. 2012; Martinez-Devesa et al. 2010; Phillips and McFerran 2010).

OUTLINE OF THE THESIS

In this thesis diagnostic and therapeutic aspects of tinnitus are assessed, based on the notion that tinnitus most probably arises from hyperactivity in the central nervous system.

In 2007 a multidisciplinary outpatient clinic for chronic tinnitus patients was started in the University Medical Center Utrecht. Because the patients seen at this Tinnitus Care Group form the base of the studies included in this thesis, the design and logistics of this clinic and an explorative description of these patients are depicted in **Chapter 2**. Also, baseline and follow-up measurements of tinnitus severity for the diagnostic protocol of this Tinnitus Care Group and for a group counseling are shown in this chapter.

Tinnitus is a highly prevalent syndrome with potential severe morbidity. Fortunately, only a small proportion of individuals experience problems due to their tinnitus in such a degree, that it influences their quality of life negatively. It is not known why these individuals develop more burden from the tinnitus. **Chapter 3** addresses this issue by assessing the relationship between various demographic-, health- and tinnitus factors on tinnitus severity.

Tinnitus patients are often worried about the sound they hear and often relate the symptom to potential brain disease. Explanation about the pathophysiology of tinnitus and the most probable underlying cause does not always take this stress away, and patients often request an MRI scan. Also, in the case of unilateral tinnitus the doctor might retain a certain degree of uncertainty about the diagnosis, leading to an MRI scan. The usefulness of a routine MRI scan in the diagnostic approach to tinnitus is the focus of **Chapter 4**.

Many possible treatments for tinnitus have been attempted over time. Developing insight in the role of the central auditory system in the pathophysiology of tinnitus has led to potential treatment modalities working against this assumed hyperactivity, first in the form of central acting medication and more recently in the form of local electrical brain stimulation (transcranial magnetic stimulation (TMS) or extradural electrical stimulation). A review of studies on the effect of anticonvulsants on tinnitus is the focus of **Chapter 5**. A randomized-controlled clinical trial on the effect of repetitive TMS is the focus of **Chapter 6**.

As tinnitus is a diverse and subjective symptom it is difficult to measure and for this reason different tinnitus-specific questionnaires have been developed. There is no outcome parameter which is generally accepted to be used in therapeutic studies. Most of the therapeutic studies performed so far use a Visual Analogue Scale, a Likert scale or one of these tinnitus-specific questionnaires as outcome parameter. A review of these tinnitus-specific questionnaires used in therapeutic studies is the focus of **Chapter 7**.

In **Chapter 8** we summarize our findings, discuss the limitations of this thesis and give recommendations for clinical care.

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Chapter 2

**Diagnostic Protocol Tinnitus Care Group,
Department of Otorhinolaryngology,
University Medical Center Utrecht**

INTRODUCTION

This chapter describes the logistics, content, and explorative results of the Tinnitus Care Group of the Department of Otorhinolaryngology of the University Medical Center Utrecht (UMC Utrecht). In addition, baseline and follow-up measurements of tinnitus severity for the diagnostic protocol and for a group counseling specific to our Tinnitus Care Group are shown in this chapter. The purpose of this chapter is to provide background information on the diagnostic protocol of the Tinnitus Care Group and on the patients that were assessed by the Tinnitus Care Group because the data of (part of) these patients, or a selection of these patients, were used for chapters 3, 4 and 6, and potential selection bias in these chapters because of this patient selection is discussed in chapter 8.

In June 2007, after an extensive preparation period the first tinnitus patient was seen at the Tinnitus Care Group of the UMC Utrecht. This Tinnitus Care Group is pure diagnostic-oriented and not therapy-oriented. Patients are assessed through a structured diagnostic protocol by a multidisciplinary team. Possible therapeutic options that are advised by the Tinnitus Care Group are offered through the regular ear, nose and throat (ENT)-outpatient clinic and the hearing and speech unit of the ENT-department of the UMC Utrecht.

Logistics

Patients referred by an ENT-specialist or an audiologist are deemed eligible for consultation by the Tinnitus Care Group. Patients referred by a general practitioner are first assessed at the general ENT-outpatient clinic to evaluate if assessment by the Tinnitus Care Group may be contributory and to evaluate if the patient is motivated for assessment through the Tinnitus Care Group. Patients are seen by a multidisciplinary team including an ENT-specialist/ resident, an audiologist (in training), and a psychologist. Patients come on two (sometimes three) visits for appointments with the different members of the team and for the different tests. Results are evaluated in a multidisciplinary meeting and discussed with the patient on a subsequent multidisciplinary consult. These logistics are visualized in Figure 1. As follow-up of their evaluation by the Tinnitus Care Group all patients are routinely offered a consult with the psychologist or social worker as a minimal contact intervention.

Before patients visit the Tinnitus Care Group they receive an information package containing an information brochure on the Tinnitus Care Group, questionnaires, and an information brochure on tinnitus. After the multidisciplinary consult in which the diagnostic results are discussed with the patient, patients receive a third information brochure on the psychosocial effects of tinnitus. All brochures are designed and written by the Tinnitus Care Group UMC Utrecht.

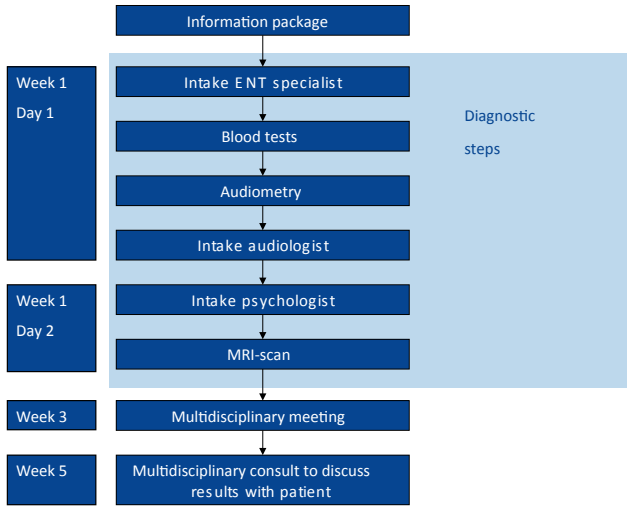


Figure 1 Example of a patient flow at the Tinnitus Care Group

Starting halfway 2010, patients were asked to fill out a questionnaire booklet containing a general open question on their experience with the Tinnitus Care Group, the Tinnitus Handicap Inventory (see section diagnostic assessment methods, subsection questionnaire booklet) and the Clinical Global Impression – improvement scale (CGI-I). The latter is a 7-point Likert scale asking the patient to score the total improvement or deterioration of their tinnitus compared to preceding their visit to the Tinnitus Care Group in: very much improved – much improved – minimally improved – no change – minimally worse – much worse – very much worse. The questionnaires were sent three months after the patient's visit to the Tinnitus Care Group.

Regular therapeutic options for tinnitus of the hearing and speech unit

Therapeutic options offered at the hearing and speech unit of the otorhinolaryngology department consist of hearing and/or masking aid fitting, and individual counseling by various disciplines (audiologist, psychologist and social worker). These professionals are all also active in the Tinnitus Care Group.

During the observation period described in this thesis one new (to our clinic) treatment option was offered. This was a group counseling by the psychologist and social worker. This group counseling, called the "Tinnitus Tips and Tricks course", is developed as a psychosocial training by the psychologist and the social worker of the Tinnitus Care Group of the UMC Utrecht. The course should be regarded as a base for psycho-education and attitude change with regard to tinnitus. The course is made up of psycho-education and cognitive behavioral therapy techniques which have been proven effective (Andersson 2002; Frenzel

et al. 1997; Tyler et al. 2007). These techniques consist of psycho-education, reflection on own choices and behavior, distraction- and relaxation techniques, concentration training, cognitive restructuring, desensitization and stress management. The content and order of the course are built according to a fixed protocol (see Table 1). The group size for the course is 6 – 12 individuals. It is given in five weekly 1½ hours meetings with a follow-up meeting after three months.

Objectives Tinnitus Care Group UMC Utrecht

The objective of the Tinnitus Care Group is to present high-quality diagnostic care to chronic tinnitus patients. Secondly, scientific research is designed in the reflection on experiences and knowledge obtained in the preparation of and the care offered through this Tinnitus Care Group. Subsequently, patients who are seen at the Tinnitus Care Group could be invited to participate in scientific research, if fulfilling a research project's inclusion criteria.

Table 1 Course program "Tinnitus Tips and Tricks course"

Session	Topics
1	Course information and acquaintance Training rationale: adaptation and coping Psycho-education: hearing, brain, behavior and stress Complaints and how to reduce them Home work: distraction
2	Psycho-education: tinnitus and distraction Diminishing tinnitus influence Sound enrichment and masking Distraction techniques Home work: a new form of distraction
3	Psycho-education: tinnitus and attention Exercise: transferring attention Exercise: breathing and relaxation Theory of diminishing attention Improvement of concentration Home work: attention techniques
4	Psycho-education: tinnitus and meaning Thoughts and feelings Options of shifting thoughts Exercise: breathing and relaxation Exercise: progressive muscle relaxation Home work: shifting thoughts
5	Psycho-education: tinnitus and relaxation Desensitization of tinnitus awareness Training tinnitus acceptance Exercise: breathing and relaxation Personality and coping styles Recapitulation Evaluation and expectations
Follow up (3 months)	Experiences Recapitulation

DIAGNOSTIC ASSESSMENT METHODS

The content of the diagnostic protocol of the Tinnitus Care Group UMC Utrecht is described below.

Questionnaire booklet

Before their first visit to the Tinnitus Care Group, patients receive a questionnaire booklet including three tinnitus-specific questionnaires (the Tinnitus Questionnaire (TQ), the Tinnitus Handicap Inventory (THI), and the Tinnitus Handicap Questionnaire (THQ)). They return the completed questionnaire booklet at their visit with the psychologist. The TQ is a 52 item self-response questionnaire with three answer possibilities (not true, partly true, true) and a total score ranging from 0 to 84 (Hallam et al. 1988). The questionnaire has five subscales: 1) cognitive and emotional distress, 2) intrusiveness, 3) auditory perceptual difficulties, 4) sleep disturbance, and 5) somatic complaints. The THI is a 25 item self-response questionnaire with three answer possibilities (no, sometimes, yes) and a score range of 0 to 100 (Newman et al. 1996). The questionnaire has three subscales: 1) functional subscale, 2) emotional subscale, 3) catastrophic subscale. The THQ is a 27 item self-response questionnaire asking the patient to score between 0 to 100 on each item (Kuk et al. 1990). It has a total score range of 0 to 2700 points. The questionnaire has three subscales: 1) physical, emotional, and social consequences of the tinnitus, 2) hearing ability, and 3) patient's view of the tinnitus. For all questionnaires higher scores account for more severe tinnitus.

Additionally, since December 2007 eleven Visual Analogue Scales (VAS) developed by the Tinnitus Care Group of the UMC Utrecht were added to the questionnaire booklet (see Figure 2). These VASs ask the patient to assess the burden of their tinnitus, to assess tinnitus characteristics (loudness, pitch, presence, and variability in pitch and/or loudness), and to assess potential problems due to tinnitus (concentration problems, sleep problems, irritation, problems in social life, problems in family life, and problems on the job/study). The VAS on burden is a visual "distress thermometer", analogous to a distress thermometer used in cancer patients, asking the patients to indicate the amount of overall distress experienced that day on an 11-point scale, ranging from 0 to 10 (no to extreme distress), with half scores when patients score in between numbers (Roth et al. 1998; Tuinman et al. 2008). The other visual analogue scales ask the patients to indicate their tinnitus characteristics and problems on a 10 cm line, ranging from 0 to 10 (no to extreme). Patients can score anywhere on the line and they are asked to rate the characteristics of each sound independently.

Medical intake

The intake with the ENT-specialist includes full history taking, questions on the tinnitus (date of onset, type of onset, pulsating character, change in perception over time), questions on hearing loss and other possible otologic complaints (vertigo, otalgia, ear fullness sensation), family history on hearing loss and tinnitus, previous treatments for tinnitus, possible other somatic complaints, general medication use and (past) ototoxic medication use, use of tobacco, alcohol or drugs, and patients are asked what their educational level and employment status is. Educational level is subdivided into high (university and higher vocational level), middle (middle vocational level, highest and middle level of high school), and low level of education (lower vocational level, lowest level of high school, elementary school). Physical examination includes otoscopy and full ENT-examination, examination of the temporomandibular joint, screening neurological examination, auscultation of neck, ears and head, blood pressure and pulse rate measurements and somatosensory test. Sixty-five to sixty-eight percent of patients have been described to be able to modulate their tinnitus through voluntary muscle contractions of predominantly the head and neck muscles (Levine 1999; Sanchez et al 2002). The somatosensory tests in our diagnostic protocol include 23 maneuvers (six jaw movements, four jaw movements against resistance, five pressure points on the head, four head movements against resistance, and four eye movements). These maneuvers were partially based on earlier described maneuvers (Coad et al. 2001; Levine 1999).

Audiometry

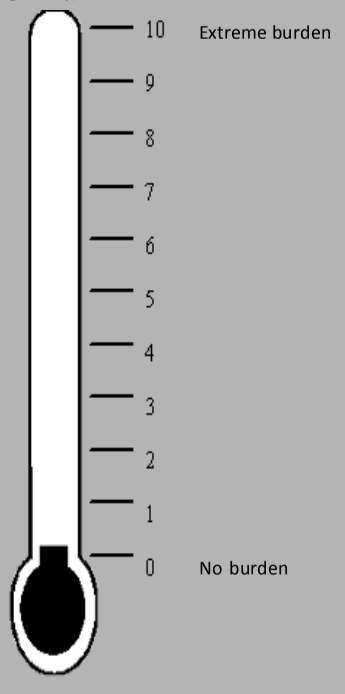
Pure-tone-audiometry, speech audiometry and tympanometry are all performed to diagnose a possible otologic cause of the tinnitus. Testing is done in a soundproof cabin with TDA 39 earphones. Pure-tone-audiometry is performed according to international standards on a Decos Audiology audiometer (Decos Technology Group, Noordwijk, the Netherlands) which is compliant with the ISO 389 standard.

Tinnitus analysis

The tinnitus analysis of the Tinnitus Care Group UMC Utrecht consists of pitch and loudness matching, measurement of minimal masking level, and measurement of complete and/or partial residual inhibition. These measures have limited diagnostic value, but they may be useful in evaluating the patient's subjective reports and in choosing and estimating the potential benefit of a hearing and/or masking aid. If a patient hears more than one sound in their tinnitus, analyses are performed for all the sounds separately. Testing is performed on the ipsilateral ear or on both ears if the tinnitus is heard inside the head. Tones are used in the analysis for tonal tinnitus and a narrow band noise (one-third of one-twelfth octave

First

Circle the number on the thermometer below that best indicates the burden that you have experienced from your tinnitus in the last week (including today).



Second

How many different sounds do you hear in your tinnitus at the moment?

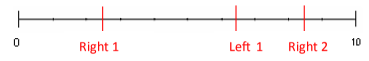
☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

Third

Indicate on the measuring rods below how your tinnitus sounds by drawing a vertical stripe through the line. You can draw the stripe anywhere on the measuring rod.

If you hear multiple sounds, draw multiple stripes on the line. Give each sound a location and a number

Example :



How loud is your tinnitus at the moment?

Inaudible — Extreme loud

0 10

How high is your tinnitus at the moment?

Extreme low — Extreme high

0 10

How much has your tinnitus been present in the last 24 hours?

Constantly absent — Constantly present

0 10

How variable (loudness and/or pitch) has your tinnitus been in the last 24 hours?

No variability — Extreme variable

0 10

Fourth

Indicate on the measuring rods below if you experienced any problems in these areas because of your tinnitus in the last week (including today). Draw a vertical stripe anywhere on the measuring rod.

Concentration

No concentration problems — Extreme concentration problems

0 10

Sleeping

No sleep problems — Extreme sleep problems

0 10

Irritation

No irritation — Extreme irritation

0 10

Social life

No problems in social life — Extreme problems in social life

0 10

Family life

No problems in family life — Extreme problems in family life

0 10

Work / study

No problems at work — Extreme problems at work

0 10

O Not applicable

Figure 2 Visual Analogue Scales used by the Tinnitus Care Group of the UMC Utrecht

band) is used for noise- or hiss-like tinnitus. Potential octave ambiguity is tested as part of tinnitus pitch matching. It has been reported that in up to 60% of patients octave confusion can be seen (Vernon and Meikle 2003). Tinnitus loudness is matched at the pitch-matched frequency. When a pitch-match cannot be obtained, the loudness is matched at 1000 Hz. Minimal masking is assessed at the tinnitus frequency. It is recorded as complete or partial masking. Residual inhibition is tested after presenting the masking sound at 10 dB above the minimal masking level for 60 seconds. It is recorded as complete or partial residual inhibition, including the duration of the residual inhibition. Residual inhibition was monitored for up to five minutes duration.

Audiological intake

Through history taking with the audiologist the following tinnitus variables are assessed: number of sounds, location, presence, tonal or noise like character, duration of burden, percentage awareness during the day, moment of the day and week with highest burden, factors possibly effecting tinnitus positively or negatively (sound, somatosensory input, nicotine, alcohol, tobacco or drugs use, stress, physical exercise, tiredness, and relaxation), and history of hearing aid or masking device use. Location is scored as unilateral (left or right), twice unilateral (distinct sounds in both ears, equally severe, more severe right, or more severe left), bilateral (same sound in both ears equally severe, more severe right, or more severe left), in the head (equal severity through entire head, more to the right, more to the left, more to the front, more to the back, more to the top), or varying locations. Additionally, the following variables are assessed on a Likert scale: pitch, co-existing problems due to tinnitus (sleep problems, concentration problems, irritation, problems in social life, problems on the job), and co-existing audiological complaints (hyperacusis and distortion of sound). The Likert scale for pitch has the following options: very high, high, medium, low or fluctuating. The other Likert scales entail the following choices: never, sometimes, regularly, often or always. Two additional variables are assessed on a 1 to 10 point Likert scale: loudness and burden.

Laboratory tests

Screening blood work is performed on full blood count, electrolytes, glucose, kidney, liver and thyroid function, lipids, zinc, albumin, CRP, immune-serology and virology screening.

Psychological intake

Patients have an orientating 1½ hour intake with the psychologist. Before this intake they complete the Symptom Checklist 90 Revised (SCL-90-R) (Derogatis 1994), MOS 36-item

Short-form Health Survey (SF-36) (Ware and Sherbourne 1992), and the Coping Inventory for Stressful Situations (CISS) (Endler and Parker 1990).

The SCL-90-R is a 90-item self-response questionnaire which can be used as a screening measure of general psychiatric symptomatology. The questionnaire asks the patient to rate the severity of each symptom over the past week on a 5-point scale ranging from 0 to 4 (not at all – extremely). The Dutch version assesses eight symptom dimensions, while the original American version has nine dimensions. The dimensions in the Dutch questionnaire are: anxiety, agoraphobia, depression, somatization, insufficiency of handling & thoughts, distrust & interpersonal sensitivity, hostility, and sleep problems (Arrindell and Ettema 2003). The overall score on the questionnaire gives an indication for psychoneuroticism. Results for each subscale are computed by adding the individual scores on each question of that subscale. Subsequently this score is compared to a norm score, leading to a 7-point interpretation of the score compared to the general population (very high, high, above average, average, below average, low, very low).

The SF-36 is a 36-item self-response questionnaire to measure the generic health status. It evaluates eight multi-item scales: physical functioning, role limitations due to physical health problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and general mental health. For each scale a raw scale score is computed which is subsequently transformed to a score on a scale of 0 to 100. Higher scores indicate a higher level of functioning or well-being. The questionnaire has been validated in Dutch (Aaronson et al. 1998).

The CISS is a 48-item self-response questionnaire to measure multidimensional coping. It asks the patients how much they engage in various types of activities on a 5-point scale ranging from 1 to 5 (not at all – very much). Three scales with coping styles are recognized: task-oriented coping, emotion-oriented coping and avoidance-oriented coping. The avoidance scale can be broken into two components: distraction and social diversion. Total scores on the subscales can be compared to norm scores for the general population (men and women separately) and categorized as very high, high, above average, average, below average, low, very low. The questionnaire has been validated in Dutch (de Ridder et al. 2004).

Diagnostic Magnetic Resonance Imaging scan

Magnetic Resonance Imaging (MRI) scans are made on a Philips 3 Tesla MRI scanner with a Sense HEAD-8 coil. The imaging protocol consists of a transverse T1-weighted (TE (time to echo in msec) = 9.09, TR (time to repetition in msec) = 2200) and T2-weighted (TE = 100, TR = 2200) screening of the whole brain in 6 mm sections. For the evaluation of the cerebellopontine angle transverse T1-weighted images with and without gadolinium contrast

(TR = 25, TE = 4.6) and T2-weighted images (TR = 4000, TE = 250) in 1.4 mm sections are used. Scans are evaluated through the routine procedures in our hospital by different radiologists.

Additional tests on indication

If a patient complains of vertigo, electronystagmography is performed. Auditory Brainstem Responses are offered in case a loop of the anterior inferior cerebellar artery in the internal auditory canal is found on the MRI scan. Computer tomography scanning is performed in patients with an unexplained conductive hearing loss. Echo-Doppler of the neck and/or Magnetic Resonance Angiography is performed in patients with a pulsatile tinnitus which is pulse-synchronous.

EXPLORATIVE DESCRIPTION OF INCLUDED PATIENTS

Three-hundred-twenty-one patients were consecutively seen at the Tinnitus Care Group of the UMC Utrecht between June 2007 and November 2012.

Demographic characteristics and medical details

Demographic characteristics are shown in table 2. The majority of the patients were male (216 male versus 105 female patients). This corresponds to reports in literature that there would be twice as many men in the group of treatment seeking patients (Henry et al. 2005). The mean age was 51 years (range 17 – 82 years). The majority of the patients had a paid job (62%) and was highly educated (52%). The tinnitus could be influenced by somatosensory modulation in 31% of patients. This is a much lower proportion than the 65 – 68% that was described in other reports (Sanchez et al. 2002; Levine 1999). Mean average (1, 2, 4 kHz) hearing threshold was 29 dBHL (range-1 – 114 dBHL).

Tinnitus characteristics

Tinnitus characteristics are shown in table 3. Mean age at tinnitus onset was 44 years (range 11 – 79 years) and the onset was as often acute (49%) as it was gradual (47%). Mean tinnitus duration was 7 years (range 2 months – 48 years). Most tinnitus either progressed over time (51%) or was unchanged (42%). The tinnitus was almost always continuously present (93%). Fifty-five percent of patients heard one sound, 29% heard two sounds, and 13% heard three sounds. The tinnitus was unilateral in 30% of patients, bilateral in 25%, twice unilateral in 13%, and was heard in the head in 24%. The tinnitus was rarely pulsating in character (15%). Most tinnitus was tonal in character (59%). This is in agreement with reports in the literature that most tinnitus is tonal, but the proportion that we found is much lower (59% versus 75 – 79%) (Eggermont 2003; Vernon and Meikle 2003). Mean matched tinnitus pitch frequency was equal to the median pitch described in literature (Stouffer and Tyler 1990; Vernon and Meikle 2003) at 6 kHz (range 100-16000 Hz). Patients judged their tinnitus moderately high on a VAS (63/100 points). Mean matched tinnitus loudness level was 51 dBHL (range 4 – 115 dBHL). Patients judged the loudness moderately high on a VAS (60/100 points). Average Sensation Level of the tinnitus (average matched loudness above the average hearing threshold) was 22 dB. This is much higher than the Sensation Level described in literature where levels lower than 9 dB are reported (Vernon and Meikle 2003). Actual matched Sensation Level was not estimated in the diagnostic protocol. It may be possible that the true matched Sensation Level is lower than the difference between the average hearing threshold and the average matched loudness level. A minority of patients did perceive variability in the pitch and/or

Table 2 Demographic characteristics and medical details

Characteristics	Number included in analyses	Mean (SD)	Number (%)
Age (years)	321	51 (12)	
Gender	321		
Male			216 (67)
Female			105 (33)
Educational level	230		
High education			119 (52)
Middle education			79 (34)
Low education			32 (14)
Employment status	321		
Employed			199 (62)
Student/housewife			11 (3)
Not employed due to tinnitus			14 (4)
Not employed other reason			35 (11)
Unemployed			14 (4)
Retired			48 (15)
Ear fullness	316		
Yes			102 (32)
No			214 (68)
Vertigo	318		
Yes			82 (26)
No			236 (74)
Otalgia	317		
Yes			49 (16)
No			268 (85)
Hyperacusis	317		
Subjective hyperacusis			
Never			117 (37)
Hardly ever			29 (9)
Sometimes			73 (23)
Often			49 (16)
UCL (dBHL)	312	105 (13)	
Distortion of sound	317		
Never			250 (79)
Hardly ever			2 (1)
Sometimes			30 (10)
Often			7 (2)
Daily			28 (9)
Somatosensory modulation	321		
Yes			100 (31)
No			221 (69)
Averaged (1, 2, 4 kHz) hearing loss (dBHL) ADS	319	29 (20)	

Table 3 Tinnitus characteristics

Characteristics	Number included in analyses	Mean (SD)	Number (%)
Age at tinnitus onset (years)		44 (12)	
Tinnitus duration (months)		85 (96)	
Number of sounds		2 (1)	
Tinnitus location	319		
Right			41 (13)
Left			56 (17)
Twice unilateral			41 (13)
Bilateral			80 (25)
In the head			77 (24)
Varying locations			24 (8)
Tinnitus type	317		
Tonal			186 (59)
Noise			122 (38)
Otherwise			9 (3)
Tinnitus onset	289		
Acute			141 (49)
Gradual			137 (47)
Unclear			11 (4)
Change in tinnitus burden over time	305		
Increased			156 (51)
Decreased			21 (7)
Unchanged			128 (42)
Tinnitus awareness during the day (0-100%)	309	76 (30)	
Tinnitus presence	307		
Continuous			284 (93)
Intermittent			23 (8)
Tinnitus pitch			
Pitch (VAS 0-100)	263	63 (24)	
Pitch (kHz, audiometric analysis)	276	5950 (4527)	
Tinnitus loudness			
Loudness (VAS 0-100)	273	60 (23)	
Loudness (dBHL, audiometric analysis)	270	51 (27)	
Tinnitus variability in loudness/pitch (VAS 0-100)	263	31 (29)	
Tinnitus Masking			
Maskability (audiometric)	317		
Yes			189 (60)
No			128 (40)
Minimal masking level (dBHL)	190	59 (26)	
Residual inhibition	314		
Yes			93 (30)
No			221 (70)
Duration residual inhibition (seconds)	93	64 (59)	

loudness of their tinnitus (VAS 31/100 points). The tinnitus could be completely or partially masked in 60% of patients and the mean minimal masking level in these patients was 59 dB HL (range 0 – 115 dBHL). There was complete or partial residual inhibition in 30% of patients and mean duration of residual inhibition was 64 seconds (range 1 second – 5 minutes = maximum observation period).

Tinnitus burden

Tinnitus burden or severity was measured on three questionnaires. Mean TQ score was 40 (SD 17, range 3 – 80), mean THI score 45 (SD 23, range 2 – 100) and mean THQ score was 1226 (SD 548, range 100 – 2550). All outcomes were normally distributed. Bivariate correlations were calculated for relationships of the three tinnitus-specific questionnaires with each other. Correlation coefficients <0.30 were considered weak, between 0.30-0.50 moderately strong and >0.50 strong (Cohen et al. 2003). All three questionnaires significantly correlated to each other (p <0.0001 for all relationships between the three questionnaires) and correlations between all questionnaires were strong and very similar (correlation coefficients ranging from 0.84 to 0.86). The THI and the THQ correlated most strongly to each other (see Figure 3). Thus, all three tinnitus-specific questionnaires seem to measure tinnitus severity quite similarly, but differences between what they exactly measure do exist.

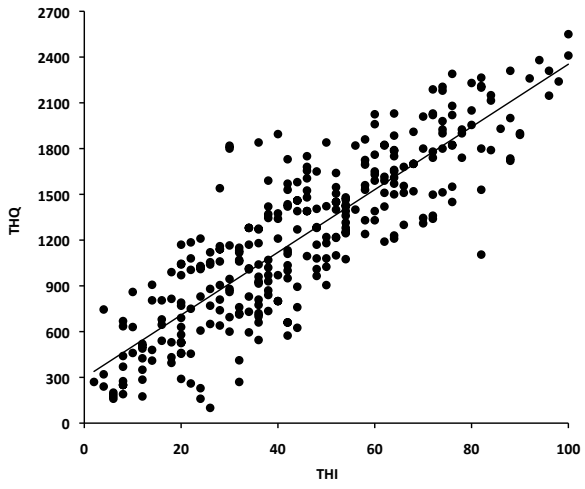


Figure 3 Scatter plot THQ versus THI for all available patients who completed both questionnaires (n=306)

Additionally, tinnitus burden was measured on a 0 – 10 Visual Analogue Scale ("distress thermometer") as well as on a 1 – 10 Likert Scale (asked by the audiologist). Both were normally distributed. Mean score on the VAS was 6.8 (SD 2.1, range 0 – 10) and mean score on the Likert scale was 6.7 (SD 2.1, range 1 – 10). These two scales significantly correlated to each other (p < 0.0001). The correlation between the two scales was strong (0.63), but surprisingly lower than would be expected from two self-assessment scales asking the same question (see Figure 4). At this point we do not have an adequate explanation for this discrepancy. Differences may arise because patients answer slightly different to a person than when filling a VAS out themselves. This cannot explain all of the discrepancy, though. Patients possibly estimated their burden only at the time-point of assessment (few days difference for VAS and Likert scale asked by audiologist) instead of on average for the past week. Or maybe sometimes the meaning of the scale was inverted (0/1 to 10 = no to extreme burden).

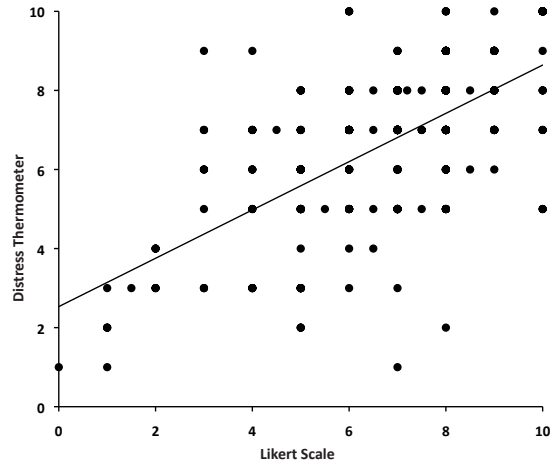


Figure 4 Scatter plot Distress Thermometer versus Likert scale for all available patients who completed both scales (n=228)

The tinnitus-specific questionnaires (TQ, THI, and THQ) and the scales (VAS and Likert) related significantly to each other (p <0.0001 for all relationships between all measurements). The correlations between the questionnaires and the scales were barely strong and smaller than the correlations for the questionnaires among each other and smaller than the correlations between the two scales (correlation coefficients 0.57 – 0.65 between the questionnaires and the VAS and 0.56 – 0.60 between the questionnaires and

the Likert scale). This could be explained by the questionnaires measuring more dimensions than burden alone.

Of the problems subjectively sensed by the patients due to tinnitus, sleep problems were experienced most often; 35% of the patients had often or daily problems in sleeping. This is lower than the 50% earlier described (Henry et al. 2005). Concentration problems were experienced frequently as well (28% often/daily and 16% regularly) and work problems were experienced regularly (20% often/daily and 13% regularly). This is more often than the 4% described earlier (Henry et al. 2005). A heightened irritation level and problems in the social interaction were experienced less often (66% and 67% did not experience any problems in these areas or only sometimes versus 16% and 18%, respectively, who experienced these problems often/daily).

Background sound was described by 62% of patients to diminish tinnitus. In 15% tinnitus was enhanced by background sound and in 11% background sound could either diminish or enhance the tinnitus. Loud sounds on the other hand enhanced the tinnitus in 48%, while 26% experienced a diminishing of the tinnitus and 26% did not experience any change. As described in the medical details, 31% of patients experienced somatosensory modulation when somatosensory tests were performed by the ENT specialist. Patients were also asked if they experienced somatosensory modulation in general. Thirty-four percent of patients responded that they did experience this modulation. Of these patients 79% experience an enhancement, in 13% the tinnitus diminishes and in 8% both effects are obtained by different modulations. Alcohol, tobacco, caffeine and drug use do not have an effect on the tinnitus in 81% of patients, in 11% the tinnitus enhances and in 4% the tinnitus diminishes. Stress enhances tinnitus in 61% and does not have an effect in 37%. Tiredness was described to either have an enhancing effect (54%) or no effect (43%). Relaxation does not have an effect in a majority of patients (42%), diminishes the tinnitus in 26% and enhances the tinnitus in 18%.

Psychological characteristics

Mean scores for the SCL-90-R, the SF-36 and the CISS are shown in table 4.

Average scores on the SCL-90-R showed that overall patients compared to the general population had high scores on all subscales and thus experience more psychiatric symptoms than the general population. The overall score for psychoneuroticism and the subscales for depression and somatization were high. Subscales for anxiety, agoraphobia, insufficiency of handling & thoughts, and sleep problems showed high/above average scores (no division between these two interpretations is available when comparing scores to a norm score for the general population). Only the subscales distrust & interpersonal sensitivity and hostility showed average scores. When compared to norm scores for chronic pain patients, tinnitus patients showed below average psychoneuroticism. All the subscales showed average scores

Table 4 Psychological characteristics

Questionnaire subscale (range)	Number included in analyses	Mean (SD)	Average norm score	Interpretation
SCL-90-R				
Anxiety	286	16 (6)	12-14	High / above average
Agoraphobia	288	9 (3)	7-8	High / above average
Depression	288	26 (10)	20-23	High
Somatization	288	21 (8)	15-18	High
Insufficiency of handling & thoughts	288	15 (6)	11-14	High / above average*
Distrust & interpersonal sensitivity	288	24 (7)	22-26	Average
Hostility	288	8 (3)	7-8	Average
Sleep problems	288	7 (4)	4-5	High / above average
Psychoneuroticism	288	137 (41)	113-123	High
SF-36				
Physical functioning	287	24 (7)	NA	70/100
Role limitations due to physical health problems	287	7 (6)	NA	75/100
Bodily pain	287	8 (4)	NA	60/100
General health perceptions	287	17 (5)	NA	60/100
Vitality	287	16 (5)	NA	60/100
Social functioning	287	8 (6)	NA	75/100
Role limitations due to emotional problems	287	6 (6)	NA	100/100
General mental health	286	22 (6)	NA	68/100
CISS				
Task-Oriented	285	M: 56 (11) F: 55 (11)	58-62 59-63	M: Below average F: Below average
Emotion-Oriented	285	M: 34 (10) F: 38 (10)	34-38 37-42	M: average F: average
Avoidance-Oriented	285	M: 40 (9) F: 45 (9)	40-44 46-50	M: average F: below average
Distraction	285	M: 18 (5) F: 21 (6)	18-19 20-23	M: average F: average
Social Diversion	285	M: 14 (4) F: 16 (4)	14-15 17-18	M: average F: below average

Average norm score = average norm score for general population, NA = not applicable, M = male, F = Female
*no division between these two interpretations is available when comparing scores to a norm score for the general population

compared to chronic pain patients, except for somatization which was below average. This indicates that the tinnitus patients seen at the Tinnitus Care Group of the UMC Utrecht are comparable to chronic pain patients in the psychiatric symptoms that they experience, although overall psychoneuroticism is a bit lower in these tinnitus patients than in chronic pain patients.

The SF-36 showed that patients had the most influence in their general health status in the scales bodily pain, general health perceptions, vitality, and general mental health. The least influence was seen in the scales role limitations due to emotional problems, social functioning, and role limitations due to physical health problems.

According to the CISS results the most often used coping strategies for men were emotion-oriented coping and avoidance-oriented coping (both on average compared to a norm population of working adults). For women the most often used coping strategy was emotion-oriented (also on average compared to a norm population of working adults). The other coping strategies (task-oriented for men and task-oriented and avoidance-oriented coping in women) were used below average compared to a norm population of working adults. When compared to a norm population of psychiatric patients, tinnitus patients (both male and female) more frequently use task-oriented coping. Women also use avoidance-oriented coping more often than psychiatric patients. Emotion-oriented coping is used less often by tinnitus patients (both men and women) compared to psychiatric patients.

RESULTS TINNITUS CARE GROUP UMC Utrecht

In this section the subjective patient experiences with the Tinnitus Care Group are provided. In addition objective baseline and follow-up measurements for the diagnostic protocol and the Tinnitus Tips and Tricks course on the subjective tinnitus severity are shown. A control group to compare these results to is not available, therefore these data have to be regarded with some caution.

Subjective patient experiences Tinnitus Care Group

One-hundred-and-forty-four patients were seen between April 2010 and November 2012. The evaluation questionnaire booklet was sent to one-hundred-twenty-three of these patients. Because of logistic reasons the questionnaire booklet was not sent to the other twenty-one patients. Seventy-five patients returned their evaluation questionnaire booklet and were included in the analyses.

Patients were generally positive about the care that they had received at the Tinnitus Care Group. Terms used to describe their experience were: good, positive, excellent, nice, and pleasant (see attachment to this thesis for original responses in Dutch). They expressed that they felt that they had been taken seriously and were glad that attention had been given to their complaint. They valued the extensive content of the diagnostic protocol, although they sometimes expressed that they had found the assessment strenuous. They commented on the staff as competent, understanding, professional, and friendly. Patients commented that they felt reassured, had gotten insight in tinnitus, and that they have more confidence or self-esteem after the assessment. If they expressed negative emotions this was generally on the fact that their tinnitus had not been cured or that there had been logistic mistakes.

Baseline and follow-up scores for the Tinnitus Care Group

The CGI-I showed that the majority of patients expressed that the tinnitus had not changed (46%) three months after visiting the Tinnitus Care Group. Thirty-eight percent of patients expressed that the tinnitus had improved and 16% expressed that the tinnitus was worse. Of the twenty-eight patients that expressed an improvement in their tinnitus, in fourteen patients (19% of the total number of patients) the tinnitus was much or very much improved and in fourteen patients (19% of the total number of patients) the tinnitus had minimally improved. Of the twelve patients that expressed that the tinnitus was worse, in four patients (5% of the total number of patients) the tinnitus was much or very much worse and in eight patients (11% of the total number of patients) the tinnitus was minimally worse.

The THI showed an improvement in scores after the visit to the Tinnitus Care Group. The mean score before visiting the Tinnitus Care Group was 45.1 (SD 22.9) for all patients. For the seventy-five patients that had returned their second questionnaire booklet the mean THI score before visiting the Tinnitus Care Group was 44.1 (SD 22.5). Three months after the visit the scores of these seventy-five patients had improved 4.5 points on average to a mean score of 39.6 (SD 23.0). This improvement was statistically weakly significant (p = 0.031, paired t-test).

Because of the lack of a control group no strong conclusions on the cause of this effect can be drawn for sure. We do not know what the effect of the natural course of tinnitus severity would have been in this group of patients and therefore do not know what the exact true effect of the diagnostic protocol would be. There is not much information available about the potential benefit of a purely diagnostic program on the severity of tinnitus. A significant effect of a similar diagnostic program (also without a control group) has been reported previously (Folmer 2002). An improvement of 5 points on the tinnitus severity index (range 0 – 48) was shown in that study six to thirty-six months after the initial tinnitus clinic appointment. It seems plausible that some patients had received some form of treatment in meantime and that therefore in some patients additional treatment affects may have been measured.

Baseline and follow-up scores for the psychosocial training (Tinnitus Tips and Tricks course)

Between January 2009 and January 2012 the Tinnitus Tips and Tricks course ran five times with forty patients in total. Twenty-four of these patients had been evaluated by the Tinnitus Care Group before the course and sixteen patients came directly from the regular ENT and audiological outpatient clinics. All forty patients completed the VAS on burden (distress thermometer) before starting the course and at the follow-up visit 3 months after completing the course. Pre-treatment mean VAS score was 6.4 (SD 1.7, range 3 – 10) and post-treatment mean VAS score was 6.0 (SD 1.5, range 3 – 9). This small improvement in burden is not statistically significant (p = 0.21, paired t-test).

All patients completed the THI at the follow-up visit as well. Patients that had not been seen by the Tinnitus Care Group also completed the THI before group treatment started. For the patients that had been seen by the Tinnitus Care Group as pre-treatment scores the THI from the pre-diagnostic stage of the Tinnitus Care Group was used. Because the period between the assessment by the Tinnitus Care Group and the Tinnitus Tips and Tricks course varies between these patients and because patients had sometimes undergone different treatment(s) in the meantime, the scores of the Tinnitus Care Group patients have to be considered with care, and the two groups cannot be pooled. As explained earlier, the THI and VAS results should be regarded with caution because a control group is not available.

Nonetheless, we do see some effects that will at least require further future investigation. Pre-treatment mean THI score for the sixteen patients in the directly referred group was 54 (SD 14, range 24 – 74) and post-treatment mean THI score for only this group of patients was 40 (SD 13, range 14 – 58). This 14 point difference in tinnitus severity is statistically significant (p = <0.0001, paired t-test) Pre-treatment score for the twenty-four Tinnitus Care Group patients was 51 (SD 20, range 4 – 86) and post-treatment mean THI score was 41 (SD 17, range 10 – 72). This 10 point difference in tinnitus severity is statistically significant (p = 0.002, paired t-test) as well. Part of this effect may be attributable to the care given by Tinnitus Care Group, because as we showed earlier, the Tinnitus Care Group led to a significant improvement of five points on average.

We cannot assess which part of this found effect is actually caused by the intervention of the Tinnitus Tips and Tricks course itself, by placebo effects, natural course effects or other unknown confounding factors. However, we may compare these in itself promising results to studies on cognitive behavioral therapy (CBT) in tinnitus patients which did use control groups. In 2010 a Cochrane review was published on the effect of CBT for treating tinnitus. It was shown that CBT reduces the global severity of tinnitus (measured with the THQ, TQ or TRQ) significantly compared to no (SMD 0.91; 95% CI 0.50 to 1.32) or other interventions (yoga, education, “minimal contact education”) (SMD 0.64; 95% CI 0.29 to 1.00) (Martinez-Devesa et al. 2010). When comparing the effect found in our study (14 points improvement = 16% improvement compared to pre-treatment score) to the improvements (for only the treatment group) found in the studies included in this review and an additional more recent trial, our results are comparable. Two of these studies use the THI as outcome measure. One shows an improvement of 11 points (21% improvement) for a seven session CBT-based self-help book guided by brief telephone support (Kaldo et al. 2007). The other study shows a 5 point improvement (13% improvement) for a specialized care program including a CBT framework (Cima et al. 2012). Other studies use either the TQ or the TRQ as outcome measures. Improvements of 14 to 40% are seen on the TQ. Fourteen percent improvement is seen in above mentioned specialized care program (Cima et al. 2012). A seven session psychophysiological intervention showed 16% improvement (Rief et al. 2005). For an eleven session CBT improvements of 29% and 33% were seen (Kroner-Herwig et al. 2003; Zachriat and Kroner-Herwig 2004), and the highest improvement (40%) was reported in a twelve session CBT and neurofeedback combination (Weise et al. 2008). A six session CBT showed a comparable high improvement (41%) on the TRQ (Andersson et al. 2005), and the earlier described study of a seven session CBT-based self-help book guided by telephone support showed a 31% improvement on the TRQ (Kaldo et al. 2007). So, although we do not have a placebo group to compare the results of our Tinnitus Tips and Tricks course to, the improvement seen seems reliable compared to earlier studies describing similar or higher effects (uncorrected for the results in their placebo group).

SUMMARY

Three-hundred-twenty-one patients were consecutively seen at the Tinnitus Care Group of the department of Otorhinolaryngology of the UMC Utrecht between June 2007 and November 2012. These patients form the basis for chapters 3, 4 and 6.

Patients were generally positive about their visits to the Tinnitus Care Group. As expected the majority did not experience an improvement in their tinnitus burden three months after visiting the Tinnitus Care Group, but a significant minority of 38% percent of patients did subjectively experience an improvement. Due to this minority the THI scores still showed a slight but statistically significant improvement after visiting the Tinnitus Care Group. A larger significant effect is obtained - by the to our clinic new treatment option of - the tinnitus Tips and Tricks group course. It is important to stipulate that these mentioned results are only measured in a cohort of patients that underwent assessment by the Tinnitus Care Group and/or the Tinnitus Tips and Tricks course. These findings should be investigated further in a prospective study with a control group.

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Chapter 3

Factors Affecting Tinnitus Severity

C.E.L. Hoekstra, F.M. Wesdorp, G.A. van Zanten, Socio-demographic, health and tinnitus related factors associated with tinnitus severity, revision submitted to Ear & Hearing

ABSTRACT

Objectives: Chronic tinnitus is a common problem that can affect the quality of life adversely. Although much has been published about factors related to severity, it remains unclear from the current literature what the most important factors are. Many relationships have only been examined once, contradicting results are reported across studies, and multivariate analyses are often not performed or could not reliably be performed because of low sample size. This study fills this void by investigating factors previously described in the literature in one study using a large enough sample size and executing univariate and multivariate analyses. The aim of this study is to examine univariate and independent effects of socio-demographic, health, and tinnitus factors on tinnitus severity by which the more vulnerable patients may be better recognized, followed-up, and/or counseled.

Design: This is a retrospective cohort study performed at the University Medical Center Utrecht in 309 consecutively seen chronic tinnitus patients. Based on results from previous research and theoretical considerations twenty-eight potential factors were included. These factors were assessed through history taking by an otorhinolaryngologist and audiologist, physical examination, audiometric tinnitus analysis, and visual analogue scales (VAS). Tinnitus severity was measured with the Tinnitus Questionnaire (TQ) and the Tinnitus Handicap Inventory (THI). Univariate and multivariate effects were analyzed.

Results: Eighteen factors related univariately with the TQ and sixteen factors related univariately with the THI. Among these, fourteen factors related univariately with both the TQ and the THI. Multivariate analysis showed three factors with an independent significant effect on both outcome parameters: percentage of tinnitus awareness during the day, self-reported depression and/or anxiety, and loudness on a VAS. Three additional factors contributed independently significantly to the explained variance on either the TQ or the THI. These factors were among the first not to reach significance on the other questionnaire: education, somatic complaints, and tinnitus variability on a VAS.

Conclusions: There is a strong relationship between tinnitus severity and percentage of tinnitus awareness during the day, self-reported depression and/or anxiety, subjectively experienced loudness, education, existence of additional somatic complaints, and subjectively experienced variability in loudness and/or pitch.

INTRODUCTION

Chronic tinnitus is a phantom auditory perception of meaningless sound in the absence of an external or internal acoustic stimulus. It is a common problem that affects 7-19% of the adult population (Axelsson and Ringdahl 1989; Chung et al. 1984; Coles 1984; Davis 1989; Nondahl et al. 2002). The majority of these individuals do not experience the tinnitus as problematic, but in up to 5% of the adult population it does lead to annoyance or even interferes with the ability to lead a normal life, and in 1-2% it affects daily life severely (Coles 1984; Davis and Rafaie 2000; Nondahl et al. 2002).

It is important to identify factors that are associated with tinnitus severity. This may contribute to a better recognition of patients at risk for high burden and might identify patients in need of follow up to monitor potential distress. In addition, the acknowledgment of these factors might be a useful tool in counseling or psychological therapies such as cognitive behavioral therapy, and therefore in the effectiveness of the care provided.

It seems likely that the (experienced) severity of tinnitus can be influenced by different factors such as socio-demographic or tinnitus characteristics or additional health complaints. Many studies over time have reported factors related to tinnitus severity (see Table 1). Among these studies many relationships have only been examined once, contradicting results are reported across studies, and reliable multivariate analyses are scarce. Combined these eighteen studies shown in table 1, identified twenty-eight factors significantly related to tinnitus severity and thirty-five factors without such a relationship. Of these twenty-eight factors, only three factors (continuous tinnitus, sleep problems, and vertigo) have been shown to significantly relate to severity in more than one study. Thirteen factors are described to both having and not having a significant relationship to severity (age, anxiety, depression, etiology, gender, hearing loss, location, loudness, loudness variability, maskability, pitch, (psycho)somatic complaints, and tinnitus type). The remaining twelve factors were reportedly significantly related to tinnitus in a single study only, namely; age at onset, avoidance, awareness, change since onset, chronic pain, controllability, hyperacusis, influence of hearing aid, internal locus of control, personality, tolerance, and various questions on quality of life.

An important drawback of the studies performed so far is that most do not include a multivariate analysis. Multivariate analyses are essential in finding uniquely related factors because these take interdependencies between different factors into account. Factors that have been found in studies only performing univariate analyses could be based on unknown confounding effects. Eleven of these studies evaluated only a small number of potential factors, and were thus able not to perform a contributory multivariate analysis (Andersson et

Table 1 Characteristics of studies assessing factors related to tinnitus severity (excluding various tinnitus questionnaires as factors).

Study	Number of patients included	Number of factors analyzed	Outcome parameter for tinnitus severity	Factors not related to severity	Factors related to severity	Factors related to severity in multiple regression analyses
Andersson 1999	39	19	K&L grading system	Hearing loss, loudness (A), duration, continuous loudness, influence of background sound, somatic problems, influence of substance or treatment, possibility to do something to ease, situations when less problematic, irritation, psychological factors, anxiety, depression, concentration difficulties	Pitch (A), minimal masking level, noise sensitivity, change since onset, avoidance, tolerance	Audiometric pitch, minimal masking level, avoidance, tolerance
Andersson 2001	146	3	TRQ	Hearing loss, loudness (A)	Maskability	Not performed
Axelsson 1989	2378	4	Likert scale	Gender	Advancing age (females), hearing loss, sleep problems	Not performed
Halford 1991	112	5	STSS	Gender, age, variability	STAI-trait, DTQ	Not performed
Henry 1995	72	5	TRQ	Pitch (A), minimal masking level, ATQ	Loudness (A), BDI	BDI
Hiller 1999	166	11	STI global score	Location, tinnitus type, pitch (S), pulsatile character, onset, 9 types of etiology	Hearing loss, continuous tinnitus, maskability, progressive loudness, SCL-90-R scales, 2 types of etiology (sudden hearing loss, craniomandibular dysfunction)	Not performed
Hiller 2006	4995	10	Mini-TQ	Duration, familial status	Gender, age, hearing loss, progressive tinnitus, location, continuous tinnitus, vertigo, hyperacusis	Not performed
Holgers 2005	127	13*	Own criteria for "tinnitus sufferer"	Gender, age, duration, hearing loss, BMI, marital status, educational level, income level, professional status, alcohol, tobacco	Various questions on NHP, mental disorders (mostly anxiety)	3 questions on NHP (find it hard to reach for things, finding live not worth living, bad sleep)
Mazurek 2010	531	3	TQ	Gender	Hearing loss, location	Not performed
Meric 1998	281	5	TRQ, THQ STSS	Gender, age, duration	Hearing loss, MMPI	Not performed
Mondelli 2011	100	3	THI	Gender, age, hearing loss	-	Not performed
Ooms 2011a	136	3	THI	Pitch (A), loudness (A), BDI-II	-	Not performed
Ooms 2011b	71	6	THI	Pitch (A), loudness (A)	STAI-state, STAI-trait, somatic anxiety	Not performed
Pinto 2010	68	3	THI	Gender, age, hearing loss	-	Not performed
Schlee 2011	755	1	Mini-TQ		Age at onset	Not performed
Scott 1990	3372	18	Likert scale	Duration, onset, location, hearing loss	Tinnitus type, 9 psychosomatic complaints maskability, presence, controllability, loudness variation	Tinnitus type, 4 psychosomatic complaints (depression, lack of concentration, insomnia, balance disturbance), maskability, presence, controllability, loudness variation,
Unterrainer 2003	149	6	THI	Pitch (S), duration, perception as illness, comorbidity	Depression, loudness (S), internal locus of control	Not performed
Wallhäuser 2012	4705	15	Mini-TQ	Gender, age, hearing loss, duration, onset, somatic comorbidity	Awareness, location, influence of hearing aid, vertigo, chronic pain, sleep problems, depression, anxiety, somatic symptom severity	Binaural/central tinnitus, influence of hearing aid, sleep problems, chronic pain, depression, anxiety, somatic symptom severity

* 13 factors are analyzed, of which of 4 factors the individual components (different questions within a questionnaire or interview or different average hearing levels) are also analyzed separately

(A) = audiometric, ATQ = Automatic Thoughts Questionnaire, BDI = Beck Depression Index, BMI = Body Mass Index, DTQ = Depressive Tendency Questionnaire, IDI = Inferential Depression Items, K&L grading system = Klockhoff and Lindblom grading system, MMPI = Minnesota Multiphasic Personality Inventory, NHP = Nottingham Health Profile, (S) = subjective, STI = Structured Tinnitus Interview, TCQ = Tinnitus Cognitions Questionnaire, THI = Tinnitus Handicap Inventory, THQ = Tinnitus Handicap Questionnaire, TQ = Tinnitus Questionnaire, TRQ = Tinnitus Reaction Questionnaire

al. 2001; Axelsson and Ringdahl 1989; Halford and Anderson 1991; Henry and Wilson 1995; Mazurek et al. 2010; Meric et al. 1998; Mondelli and Da Rocha 2011; Ooms et al. 2011a; Ooms et al. 2011b; Pinto et al. 2010; Schlee et al. 2011). Three studies which could have performed a multivariate analysis did not include this analysis (Hiller and Goebel 1999; Hiller and Goebel 2006; Unterrainer et al. 2003). Another drawback of previous studies is that the included number of participants is not always in relation to the examined number of factors. As a rule of thumb at least ten participants are needed per factor in a model for the analysis to be reliable. Unfortunately, of the five studies including a multivariate analysis two studies do not reach the 1:10 ratio (Andersson et al. 1999; Holgers et al. 2005). The three studies including a reliable multivariate analysis show thirteen factors related to tinnitus severity, of which only depression, (psycho)somatic complaints, and sleep problems were shown in two studies to relate independently to severity (Henry and Wilson 1995; Scott et al. 1990; Wallhäusser-Franke et al. 2012).

In sum, although much has been published about factors related to severity, it remains unclear from the current literature what the most important factors are. Many relationships have only been examined once, contradicting results are reported across studies, and multivariate analyses are often not performed or could not reliably be performed because of low sample size. Our study fills this void by investigating factors previously described in the literature in one study using a large enough sample size and executing univariate and multivariate analyses. The aim of this study is to examine univariate and independent effects of socio-demographic, health, and tinnitus factors on tinnitus severity by which the more vulnerable patients may be better recognized, followed-up, and/or counseled. This study focuses on above mentioned factors because these factors are commonly evaluated in a standard outpatient visit. The results of this study may give clinicians a convenient number of risk factors for (chance for) more severe tinnitus that can easily and quickly be evaluated in the medical office or through audiometry. In addition to knowing risk factors for more severe tinnitus, clinicians will also have knowledge of factors of less interest.

MATERIALS AND METHODS

Study design and participants

This study was performed at the Tinnitus Care Group of the Otorhinolaryngology department of the University Medical Center Utrecht (UMC Utrecht) as a retrospective cohort study. Patients with tinnitus of at least two months duration were examined according to a structured diagnostic protocol. All patient data collected through this protocol were anonymized and entered in an Access data base. A selection of these routinely collected data from all consecutively seen chronic tinnitus patients between June 2007 and November 2012 was included in this study. The study was performed in accordance with the Declaration of Helsinki. Because this is a retrospective study with anonymized data, exemption for a full review from the Local Research Ethics Committee was obtained (12-611/C).

Dependent variable (outcome measure)

As part of their evaluation by the Tinnitus Care Group patients completed two questionnaires to measure tinnitus severity: the Tinnitus Questionnaire (TQ) and the Tinnitus Handicap Inventory (THI). The TQ is a 52 item self-response questionnaire with three answer possibilities (not true, partly true, true) and a total score ranging from 0 to 84 (Hallam et al. 1988). The THI is a 25 item self-response questionnaire with three answer possibilities (no, sometimes, yes) and a score range of 0 to 100 (Newman et al. 1996). For both the TQ and the THI higher scores account for more severe tinnitus. Since there is no standard definition or measurement for tinnitus severity, both questionnaires are included in this study. This allows to find potential similarities or differences in the results that might arise from using different ways to measure severity.

Independent variables

Table 1 shows twenty-eight factors previously described to possibly be related to tinnitus severity. Of these factors seventeen can be defined as socio-demographic, health or tinnitus related and can easily be assessed by clinicians in the medical office or by audiometry. The following twelve of these factors were included in this study through history taking by an otorhinolaryngologist or audiologist (age, age at onset, awareness, change in perception over time, gender, hyperacusis, location, masking, pain (diagnosed pain syndrome, head, neck or other pain), type, somatic complaints, and vertigo). To measure awareness patients were asked to rate their awareness of tinnitus in percentage during the day (Stouffer and Tyler 1990). Hyperacusis was assessed subjectively on a 5-point Likert scale (“never”, “hardly ever”, “sometimes”, “often”, “daily”) and objectively as Uncomfortable Loudness Level (UCL).

Multiple measurements for masking were included because it can be measured in different ways, and has been measured differently in earlier studies. Masking was assessed through a yes/no question by the audiologist as “masking by external sounds”, audiometrically as yes/no, and audiometrically as minimal masking level. Somatic complaints (possible range 0-46) were assessed through a standard list including 9 questions concerning auto-immune disease, 11 neurologic disease complaints, 4 infectious disease complaints, 2 temporomandibular dysfunction or dental complaints, 12 metabolic or endocrine disease complaints, 8 cardiovascular disease complaints, and 2 on pain). Four of these seventeen factors were assessed on a Visual Analogue Scale (VAS) through the questionnaire booklet mentioned before. The VAS-scores were assessed on a 10cm line ranging from 0-10: loudness (inaudible to extremely loud), pitch (extremely low to extremely high), presence (continuously absent to continuously present), and variability in loudness and/or pitch (no variability to extreme variability). Because loudness and pitch have been measured differently in earlier studies we also included audiometrical measurements for these factors. The last of these seventeen factors “hearing loss”, was measured audiometrically. In addition, since earlier studies suggested an important role for anxiety and depression, we included these factors as the health related factor “self-reported depression and/or anxiety”. Also, patients filled out the SCL-90-R during the standard visit with the psychologist of the Tinnitus Clinic.

Ten additional factors were included that could theoretically be associated with tinnitus severity, were only once or not investigated before, form important tinnitus characterizations or form an interesting sub-categorization of tinnitus. Two of these additional factors were socio-demographic in nature: educational level and employment status. Four factors were tinnitus related; number of sounds, duration, onset, and residual inhibition (as yes/no and as duration of residual inhibition). The last four factors were health related: otalgia, ear fullness, distortion of sound, and somatosensory modulation. Somatosensory tests included 23 maneuvers (six jaw movements, four jaw movements against resistance, five pressure points on the head, four head movements against resistance, and four eye movements). This resulted in a total of twenty-eight factors included in this study.

Pure-tone-audiometry and tinnitus analysis (pitch and loudness matching, measurement of minimal masking level, and complete and/or partial residual inhibition) were all performed by one of two audiology assistants trained in tinnitus analysis. Potential octave ambiguity was tested as part of tinnitus pitch matching. Tinnitus loudness was matched at the pitch-matched frequency. When a pitch-match could not been obtained, the loudness was matched with a 1000Hz pure tone. Minimal masking was tested at the tinnitus frequency. Residual inhibition was tested 10dB above the minimal masking level. Testing was done in a soundproof cabin with TDH 39 earphones. Pure-tone-audiometry was performed according to international standards (ISO 8253-1) on a Decos Audiology audiometer (Decos Technology Group, Noordwijk, the Netherlands) which is compliant with ISO 389 standards.

Sample size

For a continuous outcome measure as used in this study at least ten participants are needed per factor in the model for the analyses to be reliable. Thus, using twenty-eight factors, at least two-hundred-and-eighty participants are needed.

Data analysis

Statistical analyses were conducted with SPSS 20.0 (IBM, Armonk, NY, USA). Descriptive analyses were calculated for the socio-demographic, health, and tinnitus factors. Univariate effects of tinnitus severity (TQ and THI) were explored through independent-sample t-tests for dichotomous factors and through analysis of variance (ANOVA’s) for ordinal factors. Effect sizes were computed using Cohen’s d to examine clinical significance of differences found between groups. Effect sizes ≥0.80 reflected a large clinically relevant difference, those between 0.50-0.80 were considered moderately large, and those between 0.20-0.49 were considered small (Cohen 1988). Bonferroni post-hoc tests were executed as part of the ANOVA’s to assess which groups differed significantly. For continuous factors, bivariate correlations were calculated (Pearson’s correlation for normal distributed data and Spearman’s correlations for abnormally distributed data). Correlation coefficients <0.30 were considered weak, between 0.30-0.50 moderately strong and >0.50 strong (Cohen et al. 2003). Socio-demographic, health, and tinnitus factors showing a univariate significant relationship with tinnitus severity were entered into two separate stepwise multiple regression analyses to examine unique predictive effects. The first analysis used the TQ as dependent factor; the second analysis used the THI as dependent factor. P values ≤0.05 were defined as statistically significant.

RESULTS

Patient characteristics

Three-hundred-twenty-one patients were consecutively seen at the Tinnitus Care Group of the UMC Utrecht between June 2007 and November 2012. Twelve patients had to be excluded because they had not returned their questionnaire booklet and thus no TQ or THI score was available. Therefore, a total of 309 patients were included in this study, consisting of 208 male and 101 female patients, with a mean age of 51 years (range 17-82 years). Mean tinnitus duration was 7 years (range 2 months – 48 years), mean matched tinnitus pitch was 6 kHz (range 100-16000 Hz) and mean matched tinnitus loudness was 51 dB HL (range 4-115 dB HL).

Overall completeness of data was high, in total 3% of data were missing. Response was low on one factor (educational level, 71%). Response varied between 90-94% on four factors (onset, pitch on a VAS, variability on VAS, and presence on a VAS), between 95-99% on seventeen factors, and all data was available for fourteen factors. Total numbers can be found in Table 2-4. Tinnitus analysis was performed in all 309 patients but audiometric pitch and loudness matches were not always measurable (in 270 and 264 patients respectively). Because the VAS-scores were included from December 2007, the maximum number of possible respondents for these factors was 281 patients.

Tinnitus severity

Mean TQ score was 40 (SD 17, range 3-80) and mean THI score 45 (SD 23, range 2-100), see Figures 1 and 2. Both outcomes were distributed normally and related significantly with each other (r=0.85, strong relationship).

Univariate relationships between demographic characteristics and tinnitus severity

Table 2 shows the univariate effects of demographic characteristics on tinnitus severity. Age and gender were not significantly associated with tinnitus severity. A significant effect was found for educational level and employment status on tinnitus severity. Consequent Bonferroni tests on educational level showed that all three groups differed significantly from each other on both questionnaires. The largest difference is found between patients with low and high education: patients with low education reported significantly lower TQ and THI scores than patients with high education (large effect sizes: 1.40 and 0.81 respectively). Bonferroni post-hoc test on employment status showed that employed patients reported significantly lower TQ scores than patients who are not employed because of tinnitus or because of another

Table 2 Patient characteristics, descriptives on and univariate relationships with tinnitus severity

Characteristics	Number included in analyses	Number (%) or mean±SD	TQ (mean±SD)	Univariate test		THI (mean±SD)	Univariate test	
				Test statistic	p		Test statistic	p
Age	309	51±12		r=0.1	ns		r=-0.01	ns
Gender	309			t=-1.4	ns		t=-1.3	ns
Male		208 (67)	39+17			44+23		
Female		101 (33)	42+17			47+22		
Educational level	220			F=-22.5	**p=<0.0005**		F=11.5	**p=<0.0005**
High education		29 (13)	54+15			60+26		
Middle education		77 (35)	41+16			48+22		
Low education		114 (52)	33+14			39+21		
Employment status	309			F=7.9	**p=<0.0005**		F=6.5	**p=<0.0005**
Employed		194 (63)	36+15			41+21		
Student/housewife		9 (3)	40+17			44+22		
Not employed due to tinnitus		12 (4)	49+15			54+15		
Not employed other reason		34 (11)	52+16			62+24		
Unemployed		13 (4)	45+19			55+27		
Retired		47 (15)	43+17			46+25		

Bonferroni post-hoc test educational level TQ/THI: patients with low education reported significantly lower TQ and THI scores than patients with middle education. Both these groups reported lower TQ and THI scores than high educated patients
Bonferroni post-hoc test employment status TQ: employed patients reported significantly lower TQ scores than patients who are not employed due to tinnitus or another reason.
Bonferroni post-hoc test employment status THI: employed patients and pensioned patients reported significantly lower TQ scores than patients who are not employed due to another reason

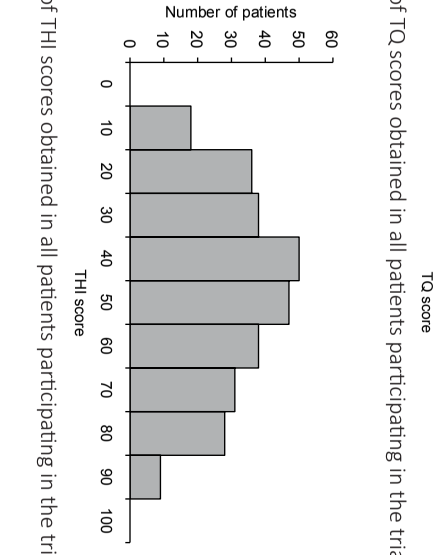

Figure 1 Distribution of TQ scores obtained in all patients participating in the trial.

Figure 2 Distribution of THI scores obtained in all patients participating in the trial.

reason than tinnitus (large effect sizes: 0.81 and 1.0 respectively). Bonferroni post-hoc tests on the THI showed that employed patients and retired patients reported significantly lower THI scores than patients who are not employed because of another reason than tinnitus (effect sizes: 0.88 (large) and 0.64 (moderate) respectively).

Univariate relationships between tinnitus factors and tinnitus severity

Nine tinnitus factors related significantly to tinnitus severity if measured using the TQ (see table 3). Four of these factors related (moderately) strongly to severity; longer tinnitus duration, number of sounds, higher percentage of awareness during the day, and louder tinnitus on a VAS. Weak correlations or small effect sizes were found with increased perception of tinnitus over time (effect size 0.29), higher tinnitus pitch on a VAS, more variable tinnitus on a VAS, higher minimal masking level, and no masking through background sounds (effect size 0.44). When measuring severity using the THI, relationships with the same factors were found, except for tinnitus duration and minimal masking level. Effect sizes and relationship strengths were similar for the seven factors that related both to the TQ and the THI.

Univariate relationships between health factors and tinnitus severity

Table 4 shows relationships between health factors and tinnitus severity. Nine health factors related significantly to tinnitus severity if measured on the TQ. A large effect size was found

Table 3 Tinnitus characteristics, descriptives on and univariate relationships with tinnitus severity

Characteristics	Number included in analyses	Number (%) or mean±SD	TQ (mean±SD)	Univariate test		THI (mean±SD)	Univariate test	
				Test statistic	p		Test statistic	p
Age at onset	301	44±12		*r*=0.03	ns		*r*=-0.07	ns
Duration (months)	301	85±97		*r*=0.1	**p=0.045**		*r*=0.1	ns
Number of sounds	308	2±1		*r*=0.1	**p=0.009**		*r*=0.2	**p=0.005**
Location	308			*F*=1.0	ns		*F*=0.8	ns
Right		40 (13)	40+16			41±21		
Left		54 (18)	38+18			41±24		
2x unilateral		40 (12)	42+16			47±24		
Bilateral		77 (25)	39+17			47±22		
In the head		73 (24)	41+17			48±24		
Varying locations		24 (8)	34+12			44±19		
Type	299			*t*=-1.9	ns		*t*=-1.3	ns
Tonal		180 (60)	38+16			43±22		
Noise		119 (40)	42+17			47±24		
Onset	278			*F*=0.7	ns		*F*=0.4	ns
Acute		136 (49)	41+16			46±22		
Gradual		131 (47)	38+17			44±24		
Unknown		11 (4)	41+18			48±24		
Change in perception over time	293			*F*=4.5	**p=0.012**		*F*=3.6	**p=0.03**
Increased		145 (50)	42+17			49±23		
Decreased		21 (7)	36+16			37±18		
Unchanged		127 (43)	37+17			43±24		
Awareness during the day	298	76±31		*r*=0.4	**p=<0.0005**		*r*=0.3	**p=<0.0005**
Presence (VAS)	264	8±2		*r*=0.1	ns		*r*=0.1	ns
Pitch								
Pitch (VAS)	262	6±2		*r*=0.2	**p=0.001**		*r*=0.2	**p=0.014**
Pitch (kHz) * (audiometric analysis)	270	6.0±4.6		*r*=-0.1	ns		*r*=-0.06	ns
Loudness								
Loudness (VAS)	272	6±2		*r*=0.4	**p=<0.0005**		*r*=0.3	**p=<0.0005**
Loudness (dB HL) (audiometric analysis)	264	51±27		*r*=0.1	ns		*r*=0.006	ns

Continuation of **table 3**

Characteristics	Number included in analyses	Number (%) or mean±SD	TQ (mean±SD)	Univariate test		THI (mean±SD)	Univariate test	
				Test statistic	p		Test statistic	p
Variability of sound (VAS)	262	3±3		*r*=0.1	**p=0.045**		*r*=0.2	**p=0.001**
Masking								
Maskability (by external sounds)	308			*t*=-3.5	**p=0.001**		*t*=-2.7	**p=0.007**
Yes		182 (59)	37+16			42±22		
No		126 (41)	44+16			49±23		
Maskability (audiometric)	307			*t*=-0.8	ns		*t*=-1.1	ns
Yes		186	39+16			44±23		
No		121	41+17			47±23		
Minimal masking level (dB)		59±26		*r*=0.2	**p=0.011**		*r*=0.06	ns
Residual inhibition	304			*t*=-0.6	ns		*t*=-1.1	ns
Yes		93 (31)	39+16			43±22		
No		211 (69)	40+17			46±23		
Duration residual inhibition (seconds)		64±59		*r*=-0.1	ns		*r*=-0.02	ns

* 309 patients pitch matching in performed, no pitch measurable in 39 patients

** 309 patients loudness matching in performed, no loudness measurable in 45 patients

Bonferroni post-hoc test change in tinnitus perception over time TQ: patients reporting unchanged tinnitus showed significantly lower TQ scores than patients reporting increased tinnitus

Bonferroni post-hoc test change in tinnitus perception over time THI: no significant differences between two of the groups

for distortion of sounds (1.12 difference between patients having never and often distortion of sounds). Moderately strong relationships or moderately large effect sizes were found for number of somatic complaints, hearing loss, self-reported depression and/or anxiety (effect size 0.75), and hyperacusis (0.71 difference between patients with never and often having hyperacusis, 0.59 difference between patients with sometimes hyperacusis and often having hyperacusis). Small effect sizes were found for pain (effect size 0.35), and vertigo (effect size 0.44). When severity was measured using the THI, the same factors related univariately significantly with increased severity except for distortion of sounds. Effect sizes and relationship strengths were comparable for the seven factors that related both to the TQ and the THI. In addition when severity was measured on the THI, a significant relationship was found with presence of ear fullness and otalgia (small effect sizes: 0.39 and 0.28 respectively).

Multivariate model predicting tinnitus severity

The factors that significantly univariately related to severity were entered in two separate stepwise multivariate models. Eighteen factors were found in the univariate analyses to significantly relate to the TQ, three with a strong effect/relationship, six with a moderate effect/relationship, and nine with a small effect or weak relationship. Sixteen factors were found in the univariate analyses to significantly relate to the THI, three with a strong effect/relationship, five with a moderate effect/relationship, and eight with a small effect or weak relationship. Fourteen factors were found to relate to both the THI and the THQ. Thus eighteen factors were included in the model using the TQ, and sixteen in the model using the THI. Employment status was dichotomized according to the outcomes of the Bonferroni post-hoc tests into "not/unemployed" versus "working/pension/students/housewives". Stepwise multiple regression analysis on the TQ showed that four factors had a significant unique predictive effect on tinnitus severity, explaining 53% of the variance (see Table 5). Analysis using the THI as dependent factor showed that five factors had a significant unique predictive effect explaining 40% of the variance (see Table 6). Three factors contributed significantly independently to the explained variance in both models: percentage awareness during the day, self-reported depression and/or anxiety, and loudness measured on a VAS. The model based on the TQ included education as well. This was the first excluded factor in the THI model (p=0.07). The model based on the THI also included somatic complaints and variability measured on a VAS. These were the second and sixth excluded factors in the TQ model (p=0.12, p=0.26 respectively). Percentage awareness of tinnitus during the day was the strongest contributing factor for tinnitus severity in both models, accounting for 30% in the explained variance in the TQ and for 16% in the THI.

Table 4 Health characteristics, descriptives on and univariate relationships with tinnitus severity

Characteristics	Number included in analyses	Number (%) or mean±SD	TQ (mean±SD)	Univariate test		THI (mean±SD)	Univariate test	
				Test statistic	p		Test statistic	p
Self-reported depression and/or anxiety	304			*t*=6.1	**p=<0.0005**		*t*=7.2	**p=<0.0005**
Yes		74 (24)	49±16			60±21		
No		230 (76)	37±16			40±21		
Pain complaints	306			*t*=3.1	**p=0.002**		*t*=3.7	**p=<0.0005**
Yes		143 (47)	43±17			50±23		
No		163 (53)	37±16			41±22		
Somatic complaints	306	4±4 (306)		*r*=0.3	**p=<0.0005**		*r*=0.3	**p=<0.0005**
Vertigo	306			*t*=3.7	**p=<0.0005**		*t*=3.1	**p=0.002**
Yes		81 (27)	45±16			52±24		
No		225 (74)	38±16			43±22		
Otalgia	305			*t*=2.1	ns		*t*=2.6	**p=0.01**
Yes		47 (15)	44±17			53±22		
No		258 (85)	39±16			44±23		
Ear fullness	304			*t*=1.4	ns		*t*=2.8	**p=0.005**
Yes		100 (33)	41±18			50±25		
No		204 (67)	39±16			43±21		
Hyperacusis								
Subjective hyperacusis	306			*F*=4.8	**p=0.001**		*F*=4.3	**p=0.002**
Never		110 (36)	36±16			40±23		
Hardly ever		29 (10)	41±15			47±21		
Sometimes		72 (24)	38±16			42±23		
Often		46 (15)	48±17			54±23		
Daily		49 (16)	42±17			51±21		
Uncomfortable Loudness Level	303	103±12		*r*=-0.3	ns		*r*=-0.8	ns
Distortion of sound	306			*F*=3.0	**p=0.018**		*F*=2.2	ns
Never		240 (78)	39±17			43±23		
Hardly ever		2 (1)	44±31			55±38		
Sometimes		30 (10)	43±17			51±24		
Often		7 (2)	58±12			63±19		
Daily		27 (9)	42±12			49±20		
Somatosensory modulation	309	3±6		*r*=-0.02	ns		*r*=0.07	ns
Averaged (1, 2, 4kHz) pure-tone-hearing loss (dB HL) ADS	309	29±23		*r*=0.3	**p=<0.0005**		*r*=0.1	ns

Bonferroni post-hoc test hyperacusis TQ/THI: patients reporting often having hyperacusis showed significantly higher TQ scores than patients reporting never or sometimes having hyperacusis

Bonferroni post-hoc test distortion of sounds TQ: patients reporting often having distortion of sounds showed significantly higher TQ scores than patients reporting never having distortion of sounds

Table 5 Stepwise multiple regression analyses TQ regarding tinnitus severity

	R^2	R^2change	Beta	F change	p value
Independent significant predictor factors	0.53				
Awareness during the day		0.30	0.55	42.03	p=<0.0005
Education		0.15	0.40	26.18	p=<0.0005
Loudness (VAS)		0.04	0.23	7.18	p=0.009
Self-reported depression and/or anxiety		0.05	0.24	9.48	p=0.003
Excluded factors					
Vertigo					p=0.099
Somatic complaints					p=0.116
Minimal masking level					p=0.128
Change in perception over time					p=0.237
Distortion of sound					p=0.250
Variability (VAS)					p=0.260
Pain					p=0.263
Masking through background sound					p=0.277
Subjective hyperacusis					p=0.280
Pitch (VAS)					p=0.451
Hearing loss					p=0.584
Duration					p=0.831
Number of sounds					p=0.891
Employment status					p=0.963

Comparison for depression and/or anxiety with the SCL-90-R

The factor "self-reported depression and/or anxiety" was strongly correlated with depression (r=0.4, p=<0.0005) and anxiety (r=0.4, p=<0.0005) as measured on the SCL-90-R in this population. When the multivariate analyses were performed with the SCL-90-R subscales for depression and anxiety instead of the "self-reported depression and/or anxiety" factor, the factors found in both models hardly change. In the model using the TQ the same factors are included, but in a different ranking: 1) percentage awareness, 2) SCL-90 depression, 3) education, 4) loudness on a VAS. The explained variance increases to 0.64. In the model using the THI the same factors are included (except for education) as well, but also in a different ranking: 1) SCL-90 depression, 2) percentage awareness, 3) loudness on a VAS, 4) SCL-90 anxiety, 5) variability on a VAS. The explained variance increases to 0.63.

Table 6 Stepwise multiple regression analyses THI regarding tinnitus severity

	R^2	R^2change	Beta	F change	p value
Independent significant predictor factors	0.40				
Awareness during the day		0.16	0.41	33.80	p=<0.0005
Self-reported depression and/or anxiety		0.10	0.33	24.16	p=<0.0005
Somatic complaints		0.07	0.26	17.10	p=<0.0005
Loudness (VAS)		0.03	0.21	10.03	p=0.002
Variability (VAS)		0.02	0.14	4.86	p=0.029
Excluded factors					
Education					p=0.067
Vertigo					p=0.078
Employment status					p=0.107
Ear fullness					p=0.163
Number of sounds					p=0.164
Change in perception over time					p=0.247
Otalgia					p=0.314
Subjective hyperacusis					p=0.537
Pain					p=0.619
Masking through background sound					p=0.718
Pitch (VAS)					p=0.940

DISCUSSION

This is a retrospective study investigating socio-demographic, health and tinnitus factors that can easily be assessed by clinicians in the medical office or by audiometry. Univariate and multivariate analyses were performed to identify the factors that independently affect tinnitus severity the most. Twenty-eight factors were analyzed of which eighteen had previously been described to relate to tinnitus severity. Because this is a cross-sectional study a statement on the direction (causality) of the relationships that were found cannot be made.

Three factors were identified that have a unique significant effect on tinnitus severity when measured on both the TQ and the THI: 1) percentage of tinnitus awareness during the day, 2) self-reported depression and/or anxiety, and 3) tinnitus loudness on a VAS. Three other factors were included in one of the two models: education, somatic complaints, and tinnitus variability on a VAS. These three factors were among the first factors not to reach significance in the other model. Of these six factors, depression and (psycho)somatic complaints were previously shown to relate to severity more than once in multivariate analyses (Henry and Wilson 1995; Scott et al. 1990; Wallhäusser-Franke et al. 2012). Univariate relationships with depression and/or anxiety have been demonstrated multiple times as well (Halford and Anderson 1991; Henry and Wilson 1995; Holgers et al. 2005; Ooms et al. 2011b; Unterrainer et al. 2003; Wallhäusser-Franke et al. 2012). However, two studies did not show an effect of anxiety and/or depression (Andersson et al. 1999; Ooms et al. 2011a). Though a relationship with (psycho)somatic complaints was shown in this study and two previous studies (Scott et al. 1990; Wallhäusser-Franke et al. 2012), somatic comorbidity has previously been demonstrated not to relate to severity (Andersson et al. 1999; Unterrainer et al. 2003; Wallhäusser-Franke et al. 2012). A possible explanation could be that somatization occurs in patients with higher severity. It has been proposed that the relationship between somatic complaints and tinnitus severity is based on a larger proportion of patients with a somatoform disorder in patients who experience more severity (Wallhäusser-Franke et al. 2012). Of the remaining four factors that we found to relate to tinnitus severity, awareness and education have only been included in a single study (Holgers et al. 2005; Wallhäusser-Franke et al. 2012). The literature is ambiguous concerning the effect of variability of tinnitus and loudness (Andersson et al. 1999; Andersson et al. 2001; Halford and Anderson 1991; Henry et al. 2005; Ooms et al. 2011a; Ooms et al. 2011b; Scott et al. 1990; Unterrainer et al. 2003).

Interestingly, in this study loudness, pitch, and hyperacusis were all associated with severity when measured on a VAS or a Likert scale, but not when these factors were measured audiometrically. For loudness and pitch contradicting results have been shown in

literature. These discrepancies might be generated by the method of measurement. It can be postulated that loudness or pitch (measured audiometrically) do not relate to severity, but that experienced severity has its repercussions on the way loudness or pitch is perceived, leading to higher VAS scores. This does seem to apply for loudness, as in line with our study, five out of six studies measuring loudness audiometrically do not find a relationship (Andersson et al. 1999; Ooms et al. 2011a; Ooms et al. 2011b; Andersson et al. 2001; Halford and Anderson 1991) and one study measuring loudness subjectively does find a relationship (Unterrainer et al. 2003). As for pitch, studies reported no effect on tinnitus severity of either audiometrically (Ooms et al. 2011a; Ooms et al. 2011b) or subjectively measured pitch (Hiller and Goebel 1999; Unterrainer et al. 2003). This is in contrast to this study demonstrating an univariate relationship between subjective tinnitus pitch, and to one study finding a unique effect of audiometric pitch in multivariate analysis (Andersson et al. 1999).

Unfortunately, there is no gold standard to measure tinnitus severity. It could be possible that different results would have been reached by using other measurements for tinnitus severity, such as the Tinnitus Handicap Questionnaire (Kuk et al. 1990) or VAS or Likert scales. To partially control for this limitation, results in this study were compared between the TQ and the THI. Most results are similar for the TQ and the THI, but some discrepancies can be seen. Four factors related univariately significantly with the TQ, but not with the THI (tinnitus duration, minimal masking level, distortion of sounds, and hearing loss). Two factors related univariately significantly with the THI, but not the TQ (vertigo and otalgia). In general effect sizes of these factors were small and none of these factors had a unique significant effect on severity in the multivariate models. In the multivariate analysis three factors are found to significantly contribute in the explained variance in both models, and three factors contributed in one of the models. These three factors were among the first to be excluded from the other model. The high similarity in the outcomes for both questionnaires, coupled with the high correlation coefficient (0.85) found in the current study, indicates that both questionnaires broadly measure tinnitus severity similarly. However, small differences between what they actually measure do exist.

A limitation of this study could be the large amount of included factors in relation to the size of the study population. However, the recommended minimal ratio of 1:10 for factors per participants is adequately reached (28 factors to 309 participants). Secondly, only factors with a univariate effect were entered in the multivariate analyses. Also, verification through correction for multiple comparisons (applying $1-(1-\alpha)^{28} = 0.05$, $\alpha=0.0018$) shows that all factors that result from the multivariate analyses retain significance. A second drawback of this study is that it is a cross-sectional study and that therefore a statement on the direction (causality) of the relationships found cannot be made. Future prospective studies should focus on the factors found in this study to determine the causality of the effect.

The factor self-reported depression and/or anxiety can be more reliable measured with well-validated questionnaires. The aim of our study though, was to measure variables that are easy and quickly assessable by the clinician in the medical office, which excludes time consuming measurements as questionnaires. When the factors depression and anxiety are measured with the SCL-90 questionnaire, the factors found in both models hardly change, while the reliability increases much (from 0.53 to 0.64 for the TQ and from 0.40 to 0.63 for the THI). This indicates that for screening, the factor “self reported depression and/or anxiety” is reliable to use. When risk for more severe tinnitus is found with these factors and a patient scores on this depression and/or anxiety factor we advise that the patient would be referred to a psychologist who should then perform an intake using validated questionnaires according to their professional guidelines. Consequent tailored professional care should be given following the standards of that professional.

In sum, percentage of tinnitus awareness during the day, self-reported depression and/or anxiety, education, existence of additional somatic complaints, subjectively experienced loudness, and subjectively experienced variability in loudness and/or pitch strongly relate to tinnitus severity on one or both questionnaires (TQ, THI). Awareness during the day turned out to be the most important factor in both our models, explaining almost a fifth of the variance. Present literature confirms the significance of depression and/or anxiety complaints or somatic complaints on tinnitus severity. Opposing results are found throughout the literature for tinnitus loudness. This is possibly caused by different ways in which loudness was measured (audiometrically or through a VAS). On an individual basis by assessing these factors a clinician can identify a patient at risk for increased tinnitus severity more easily and quickly. If indeed from this assesment a prognosis for more severe tinnitus is found, it is recommended that the clinician offers the patient the option of follow-up, in order to monitor potential development of distress. In general, counseling might be improved by acknowledgement of the role these factors. Further research is needed to investigate the causal relationship between these factors and tinnitus severity.

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Chapter 4

Magnetic Resonance Imaging in Tinnitus

C.E.L. Hoekstra, V.F. Prijs, G.A. van Zanten, Diagnostic yield of routine MRI in tinnitus and clinical relevance of AICA loops, accepted by Otology & Neurotology

SUMMARY

Objective: to assess the diagnostic yield of a routine MRI scan in (unilateral) chronic tinnitus patients, to define the frequency of incidental findings, and to assess the clinical relevance of potentially found AICA loops.

Study design: retrospective cohort study

Settings: tertiary Tinnitus Care Group at the University Medical Center Utrecht

Patients: Three-hundred-twenty-one chronic tinnitus patients

Intervention: Routine diagnostic Magnetic Resonance Imaging (MRI) and diagnostic Auditory Brain stem Responses (ABR) when an AICA loop was found.

Main Outcome measure: Relationship between abnormalities on MRI and tinnitus

Results: In one-hundred-and-thirty-eight patients (45%) an abnormality on the MRI scan was described. In only seven patients (2.2%) the abnormality probably related to the patient's tinnitus. Results were not significantly better in unilateral tinnitus patients (abnormalities in 3.2%). Incidental findings, not related to the tinnitus were found in 41% of patients. In seventy patients (23%) an AICA loop was found in the internal auditory canal. No significant relationships were found between the presence of an AICA loop and the side of the tinnitus, abnormalities on the BERA or complaints specific to nerve compression syndrome.

Conclusion: A routine MRI scan is of little or no value in tinnitus patients with persistent complaints. AICA loops are often encountered on an MRI scan, but rarely relate to the tinnitus and should thus be considered incidental findings. It is advised to only perform an MRI scan when on clinical grounds a specific etiology with tinnitus as the symptom seems probable.

INTRODUCTION

Chronic tinnitus is a phantom auditory perception of meaningless sound in the absence of an external or internal acoustic stimulus. It is a common problem that affects 7-19% of the adult population (Axelsson and Ringdahl 1989; Chung et al. 1984; Coles 1984; Davis 1989a; Nondahl et al. 2002). Multiple different etiologies for tinnitus have been described. Otologic disorders, mainly sensorineural hearing loss, are said to be the most common cause of tinnitus and to be found in more than 90% of patients (Crummer and Hassan 2004; Schleuning 1991; Schwaber 2003; Stouffer and Tyler 1990). Five to ten percent of tinnitus is said to be caused by a neurological disorder such as Multiple Sclerosis (MS) or head trauma (Crummer and Hassan 2004; Lockwood et al. 2002; Peifer et al. 1999; Perry and Gantz 2000; Schleuning 1991). These numbers also include diagnoses which could be called otologic as well, such as cerebellopontine angle tumors or vascular compression of the vestibulocochlear nerve.

Magnetic Resonance Imaging (MRI) might be helpful to diagnose the cause of tinnitus, but most of the underlying (otologic) disorders do not require imaging for the diagnosis. Different recommendations on the use of MRI scans in tinnitus diagnosis have been made. The broadest recommendation suggests that many patients will require an MRI scan for the diagnosis to be made (Crummer and Hassan 2004). Most reports base their recommendations on the possibility of a cerebellopontine angle tumor. They recommend an MRI scan in patients with unilateral tinnitus and (non-specified) hearing loss (Peifer et al. 1999; Schwaber 2003), or in all unilateral tinnitus patients, irrespective of the existence of a hearing loss (Schleuning 1991). Other reports suggest that an MRI scan should only be considered based on unspecified audiometric results (Lockwood et al. 2002) or in patients with unilateral or asymmetrical hearing loss (Noell and Meyerhoff 2003).

The usefulness of a routine MRI scan in patients with tinnitus remains uncertain. The main reason to perform an MRI scan is to exclude a vestibular schwannoma. In a review of thirteen studies it was shown that a vestibular schwannoma was detected in 1.4-15% of patients that underwent an MRI scan to exclude this diagnosis (Vandervelde and Connor 2009). The diagnostic yield shows a downward trend over time, probably because of an increased referral pattern over time (Vandervelde and Connor 2009). A routine MRI scan in tinnitus patients could also be useful to find serious but less prevalent conditions causing tinnitus. Examples of these are brainstem disease (MS or Chiari 1 malformation) and microvascular damage through hypertension, diabetes or hypercholesterolemia (Branstetter and Weissman 2006). Opposing routine scanning are financial costs and the fact that it might lead to incidental, non-significant findings.

A potential uncertainty that may arise from routine MRI scanning is the presence of a vascular loop of the anterior inferior cerebellar artery (AICA) in the internal auditory canal. This has been described to potentially cause tinnitus through compression on the cochleovestibular nerve. Positive results for surgery on this symptom have been reported, though often with limited success rates of 40-77% (Brookes 1996; de Ridder et al. 2005; Guevara et al. 2008; Moller et al. 1993a; Okamura et al. 2000). AICA loops can be well recognized on an MRI scan, but discussion remains on their relationship with tinnitus. They are common in the general population and are often found without clinical implications. In cadaver studies an AICA was found to enter the internal auditory canal in 40-67% of specimens (Herzog et al. 1997). There is no universal accepted definition for this cochleovestibular nerve compression syndrome. Auditory brain stem responses (ABR) have been advised as the most sensitive test (Moller et al. 1993b). Moller's criteria state that if a cochleovestibular nerve compression syndrome is present that the ABR shows an increase in interpeak latencies (IPL) I-III of ≥ 0.2 ms in the ipsilateral recording, an increase in IPL III-IV in the contralateral recording of ≥ 0.2 ms or a peak II amplitude of <33% (de Ridder et al. 2002; Moller et al. 1993b). In studies on the cochleovestibular nerve compression syndrome ABR results have been used as proof of the diagnosis (Guevara et al. 2008; Moller et al. 1993a), but also only clinical characteristics have been used (Okamura et al. 2000), as well as a combination of clinical characteristics and results from MRI and ABR (de Ridder et al. 2002). The Tinnitus Research Initiative (TRI) has proposed diagnostic criteria to be used as a research classification (see Table 1), including both clinical characteristics and results from MRI and ABR.

The aim of our study is to assess the diagnostic yield of a routine MRI scan in (unilateral) chronic tinnitus patients, as well as to define the frequency of incidental findings. Secondly we assess the clinical relevance of potentially found AICA loops.

Table 1 Diagnostic criteria of cochleovestibular nerve compression syndrome proposed by the Tinnitus Research Initiative (www.tinnitusresearch.org)

Possible	initially intermittent unilateral spells without associated symptoms
Probable	possible syndrome with associated symptoms (otalgia, vertigo, or hemifacial spasms) or MRI demonstrating vascular compression of cochleovestibular nerve or abnormal ABR (long I-III interval, absent wave II)
Definite	probable syndrome with associated syndromes and/or abnormal ABR and/or abnormal MRI
Certain	definite syndrome with surgical proof

MRI = Magnetic Resonance Imaging, ABR = Auditory Brainstem Responses

METHODS

Study design and participants

This study was performed at the Tinnitus Care Group of the Otorhinolaryngology department of the University Medical Center Utrecht (UMC Utrecht) as a retrospective cohort study. Patients with tinnitus of at least two months duration were examined according to a structured diagnostic protocol. All patient data collected through this protocol were anonymized and entered in an Access data base. Data collected from all consecutively seen chronic tinnitus patients between June 2007 and November 2012 were included. The study was performed in accordance with the Declaration of Helsinki. Because this is a retrospective study with anonymized data, exemption for a full review from the Institutional Review Board of the UMC Utrecht was obtained (12-611/C).

Measures

Through the diagnostic protocol, the following socio-demographic, medical and tinnitus variables were obtained: age, gender, otologic complaints (vertigo, otalgia, hemifacial spasms), tinnitus duration, number of tinnitus sounds, tinnitus location, tinnitus presence (continuous or intermittent), tinnitus type (tonal or noise), and onset (acute or gradual). Tinnitus severity was measured with the Tinnitus Questionnaire (TQ) (Hallam et al. 1988) and the Tinnitus Handicap Inventory (THI) (Newman et al. 1996).

Pure-tone-audiometry and tinnitus analysis (pitch and loudness matching) were all performed by one of four audiology assistants trained in tinnitus analysis. Potential octave ambiguity was tested as part of tinnitus pitch matching. Tinnitus loudness was matched at the pitch-matched frequency. When a pitch-match could not been obtained, the loudness was matched at 1000Hz. Testing was done in a soundproof cabin with TDH 39 earphones. Pure-tone-audiometry was performed according to international standards (ISO 8253-1) on a Decos Audiology Workstation (Decos Technology Group, Noordwijk, the Netherlands) which is compliant with ISO 389 standards.

MRI scans were made on a Philips 3 Tesla MRI scanner with a Sense HEAD-8 coil. The imaging protocol consisted of a transverse T1-weighted (TE (time to echo in msec) = 9.09, TR (time to repetition in msec) = 2200) and T2-weighted (TE = 100, TR = 2200) screening of the whole brain in 6 mm sections. For the evaluation of the cerebellopontine angle transverse T1-weighted with and without gadolinium contrast (TR = 25, TE = 4.6) and T2-weighted images (TR = 4000, TE = 250) in 1.4 mm sections were used. Scans were evaluated through the normal diagnostic process in our hospital by different radiologists following their standard evaluation protocol and describing incidental findings on the brain and cerebellopontine

angle scans. Radiologists were specifically asked to look for pathology in the cochlea and/or vestibulum, in the cerebellopontine angle, for vascular pathology and for AICA loops. For the presence of an AICA loop in the internal auditory canal the Chavda classification was followed (McDermott et al. 2003). This classification has three grades: grade I = AICA loop lying within the cerebellopontine angle, but not entering the internal auditory canal, II = loop entering the internal auditory canal but not extending more than 50% of the length of the canal, III = loop extending more than 50% in the internal auditory canal. Only type II and III loops were recorded.

Auditory Brainstem Responses (ABR) were offered since October 2007 in case an AICA loop was found on the MRI scan. ABR-recording was done following conventional methods with help of a commercial Evoked Potential recording system (Synergy by Medelec, or Multiliner by Jaeger). The stimulus used was an 100µs-duration electrically-rectangular pulse, with a repetition rate of 23 Hz, with an alternating polarity, and presented via a TDH39 standard headphones, at levels of 70, 80 and 90 dBnHL or higher in case of absent peak I, up to 105 dBnHL. Fifteen hundred accepted sweeps were averaged, with artifact rejection beyond ± 20 µV. Electrode-impedances were brought and kept below 5 kOhm. Electrode signals were filtered with a pass band of 80 through 5000 Hz. Dual-channel recordings were acquired, with electrode position forehead (Fp0) connected to both the positive inputs of the differential amplifiers, Fp1 to the 0-inputs, the planum-mastoideum left (A1) and right (A2) to the negative inputs. ABR-qualities were read from the both the ipsilateral recording (that is derived between forehead and mastoid at the stimulation side) and the contralateral recording, by an experienced judge (author VFP), according to the criteria of Moller de Ridder et al. 2002; Moller et al. 1993b).

Data analysis

Statistical analyses were conducted with SPSS 20.0 (IBM, Armonk, NY, USA). Descriptive analyses were performed for the patient characteristics and for abnormalities on the MRI scan. Comparisons between groups (with versus without MRI abnormalities, unilateral versus bilateral tinnitus, with versus without an AICA loop, with versus without ABR abnormalities) were performed with chi^2 of fisher exact tests.

RESULTS

Patient characteristics

Three-hundred-twenty-one patients were consecutively seen at the Tinnitus Care Group of the UMC Utrecht between June 2007 and November 2012. Thirteen patients did not undergo an MRI scan and these patients were excluded. Reasons for not undergoing an MRI scan were: claustrophobia or other anxiety problems (seven patients), patient refusal (four patients), a recent MRI scan in a different hospital and a medical reason. Therefore 308 patients in total were included in this study, consisting of 209 male and 99 female patients, with a mean age of 51 years (range 17 – 82 years). Demographic characteristics of the included population are shown in Table 2. For almost all patients all data was available; for most characteristics for less than ten patients at most data were missing. Information was not available on the onset of tinnitus in thirty patients, probably because they had found it too difficult to remember. Mean tinnitus duration was 7 years (range 2 months – 48 years), mean matched tinnitus pitch was 6 kHz (range 100 Hz – 16 kHz) and mean matched tinnitus loudness level was 51 dB HL (range 4 – 115 dB HL).

Abnormalities on MRI scan

In one-hundred-and-thirty-eight patients (45%) an abnormality on the MRI scan was described (see Table 3). Most often an AICA loop in the internal auditory canal was found (23%). The second most common abnormalities were found in the cerebrum in fifty-three patients (19%). These were most often age-related effects (15% of patients). Third most common abnormalities that were found were of a vascular nature, either a high riding jugular bulb or an abnormal caliber of vessels (9% of patients).

In seven patients (2.2%) an abnormality probably related to the patient's tinnitus was found on the MRI scan. None of the findings however, directly influenced the individual patient's diagnosis of the tinnitus. In two patients a vestibular schwannoma was found, but the presence of this schwannoma was already known before this MRI scan. In two patients the abnormalities on the MRI scan corroborated a hypothesis for the diagnosis. In one patient it was thought, based on the onset history that the tinnitus was most probably caused by a vascular incident. The MRI scan showed multiple old vascular incidents, making this diagnosis more plausible. In another patient Menière's disease was considered. Because the MRI scan and subsequent CT scan showed a partial sclerosis of the posterior semicircular canal, it was deemed more plausible that the patient suffered from endolymphatic hydrops due to a labyrinthitis in the past (for which there were indications in the history) than from Menière's disease. In three patients the findings on the MRI scan matched the diagnosis. All three

Table 2 Characteristics of included patients

Characteristics	Number included in analyses	Mean ± SD	Number (%)
Age	308	51 ± 12	
Gender	308		
Male			209 (68)
Female			99 (32)
Tinnitus duration (years)	300	7 ± 8	
Onset	278		
Acute			134 (48)
Gradual			133 (48)
Unknown			11 (4)
Number of sounds	307	1.7 ± 1.0	
Tinnitus presence	306		
Continuous			283 (93)
Intermittent			23 (8)
Localization	306		
Unilateral‡			92 (30) [38: 54]
2x unilateral			41 (13)
Bilateral			77 (25)
In the head			75 (25)
Varying locations			21 (7)
Tinnitus type	305		
Tonal			178 (58)
Noise			117 (38)
Other			10 (3)
Vertigo	306		
No			228 (75)
Yes			78 (26)
Otalgia	305		
No			258 (85)
Yes			17 (15)
Hemifacial spasm	303		
No			281 (93)
Yes			21 (7)
Tinnitus Questionnaire	296	39 ± 17	
Tinnitus Handicap Inventory	296	45 ± 23	
Averaged (1, 2, 4 kHz) pure-tone-hearing loss (dB)	308	28 ± 23	
Asymmetrical hearing loss (≥ 15 dB difference)	308		70 (23)
Matched tinnitus pitch (Hz)	265*	5970 ± 4520	
Matched tinnitus loudness (dB HL)	259**	51 ± 27	

‡ values in square brackets denote right:left ratio
* In 308 patients pitch matching was performed, no pitch measurable in 43 patients
** In 308 patients loudness matching was performed, no loudness measurable in 49 patients

patients suffered a total hearing loss after head trauma and the MRI scan showed evidence of this trauma (no fluid content in cochlea and/or vestibulum or contusion focus in the brain). This diagnosis would, however, have been made without the MRI scan as well and therefore the MRI scan was not deemed contributory to the diagnosis.

In fifteen patients a potential clinical significant abnormality, irrelevant to the tinnitus was found. In nine patients a tumor was identified: six times an arachnoid cyst, once a lipoma, once a calcified meningioma and once a cavernoma. All did not require treatment or follow-up. In three patients an abnormality was encountered that required a follow-up scan after six months or an additional CT scan (hyperintense lesion in the petrous bone, hyperintense lesion in the internal auditory canal and an uncommonly widened perivascular space). All follow-up scans did not show any significant abnormalities. Three patients showed an abnormality which required referral to another specialist: one brain injury, one lesion in the sella turcica and one lesion in the pituitary gland. The patient with the brain injury required treatment by a rehabilitation physician, the other two did not require treatment or follow-up.

In one-hundred-nineteen patients the tinnitus was unilateral (including tinnitus unilaterally located in the head) and in one-hundred-sixty-three patients the tinnitus was bilateral (including tinnitus bilaterally located in the head). In fifty-eight unilateral patients an MRI abnormality was found and in sixty-nine bilateral patients. There was no significant relationship between presence of an abnormality on the MRI scan between patients with unilateral or bilateral tinnitus (p = 0.29). The patients in which an abnormality was found to be related to the patient's tinnitus had significantly more often unilateral tinnitus (p = 0.044). In six of these seven patients the tinnitus was unilateral.

AICA loops

In seventy patients (23%) an AICA loop was found in the internal auditory canal. In thirty-nine of these patients the tinnitus was described as predominantly right- or left-sided (see Table 4). The side of the AICA loop was not significantly correlated to the side of the tinnitus. An AICA loop on the right side was encountered in eight patients with right-sided tinnitus and in ten patients with left-sided tinnitus (p = 0.88). An AICA loop on the left side was encountered in ten patients with left-sided tinnitus and in eleven patients with right-sided tinnitus (p = 0.33).

Forty-five of the seventy patients with an AICA loop underwent an ABR test. Twenty-five patients did not undergo an ABR test: four patients were seen before the ABR test was routinely offered, two patients refused the ABR test and in nineteen patients an ABR test was not offered because of various reasons (AICA loop opposite to the tinnitus side, very low tinnitus burden and thus an indication not to perform additional tests, other main complaint, or unclear reasons). Of the forty-five patients who underwent an ABR test, eighteen patients showed ABR abnormalities on the side of the AICA loop. One patient showed abnormalities

Table 3 Abnormalities on Magnetic Resonance Imaging scan

Characteristics	No abnormalities (%)	Abnormalities (%)	Abnormality related to tinnitus
Total number of abnormalities		138 (44.8)	
Cerebrum	250 (81.2)		1 patient
Arachnoid cyst		3 (1.0)	2 patients
Calcified meningioma		1 (0.3)	
Cavernoma		1 (0.3)	
Lipoma		1 (0.3)	
Age related effects (e.g. minor vascular damage, atrophy, widened perivascular space)		47 (15.3)	
Post traumatic damage / contusion		3 (1.0)	
(Metal) artifacts		2 (0.6)	
Cerebellum	304 (98.7)		
Arachnoid cyst		1 (0.3)	
Age related effects (minor vascular damage)		2 (0.6)	
Venous development anomaly		1 (0.3)	
Brainstem	306 (99.4)		
Age related effects (minor vascular damage)		1 (0.3)	
Venous development anomaly		1 (0.3)	
Mastoid	304 (98.7)		
Mucous swelling		4 (1.3)	
Cochlea	307 (99.7)		
Obliterative changes		1 (0.3)	1 patient
Vestibulum	305 (99.0)		
Obliterative changes		3 (1.0)	1 patient
Internal auditory canal	236 (76.6)		
Vestibular schwannoma		1 (0.3)	1 patient
AICA loop		70 (22.7)	
Small hyperintense dot, probably vascular nature*		1 (0.3)	
Cerebellopontine angle	304 (98.7)		
Arachnoid cyst		3 (1.0)	
Vestibular schwannoma		1 (0.3)	1 patient
Vascular	281 (91.2)		
High riding jugular bulb		19 (6.2)	
Abnormal caliber		7 (2.3)	
Abnormal lumen		1 (0.3)	
Other regions	305 (99.0)		
Cystic lesion sella turcica		1 (0.3)	
Hyperintense lesion near the skull base**		1 (0.3)	
Not functioning adenoma pitituary gland		1 (0.3)	

AICA = Anterior Inferior Cerebellar Artery
* control scan after 6 months did not replicate the abnormality
** computed tomography scan showed mucous swelling in the petrous bone

fulfilling all three of Moller's criteria, three patients showed two of these abnormalities and the other fourteen showed one abnormality. Of these eighteen patients six patients also showed ABR abnormalities on the contralateral side of the AICA loop (two had more abnormalities on the contralateral than the ipsilateral side). Abnormalities found on the ABR test were not significantly related to the side of the AICA loop (p = 0.22). In total, seventeen patients showed ABR abnormalities on the contralateral side. Complaints which have been described to be specific to the cochleovestibular nerve compression syndrome were not related to the presence of an AICA loop (unilateral hearing loss, p = 0.29; otalgia, p = 0.18; vertigo, p = 0.48; hemifacial spasm, p = 0.85)

Sixty-seven of the seventy patients with an AICA loop did not meet the criteria for a definite cochleovestibular nerve compression syndrome according to the diagnostic criteria of the TRI (www.tinnitusresearch.org). Twenty-one patients had bilateral tinnitus, a continuous tinnitus without initial spells, or associated symptoms on presentation, therefore not complying with a possible syndrome. Thirty-one patients did not have accompanying complaints and in fourteen patients the ABR was normal. Thus, we showed a definite syndrome in three patients according to the criteria of the TRI.

Table 4 Anterior Inferior Cerebellar Artery AICA loop in the internal auditory canal

	AICA loop right side	AICA loop left side
Right sided tinnitus	8	11
Left sided tinnitus	10	10
p-value	0.88	0.33

DISCUSSION

In this study we showed that in 2.2% of three-hundred-eight patients an abnormality possibly related to the patient's tinnitus was found on a routine MRI scan. Incidental findings, not related to the tinnitus were found in 41% of patients. The patients with possibly tinnitus related MRI-abnormalities had significantly more often unilateral tinnitus. However, overall results were not much better for the total group of patients with unilateral tinnitus. In only 3.2% of unilateral tinnitus patients related MRI abnormalities were found and incidental MRI-abnormalities were encountered in 48% of patients.

It remains debatable if unilateral tinnitus without hearing loss should form an indication to screen for a vestibular schwannoma. Tinnitus without hearing loss has been shown to be present in 4% of vestibular schwannoma patients (Berrettni et al. 1997). Also, in a group of patients with a vestibular schwannoma without hearing loss, tinnitus was shown to be the presenting symptom in 14% of these patients (Lustig et al. 1998). It has thus been recommended to screen unilateral tinnitus patients without hearing loss for vestibular schwannoma (Gimsing 2010), although the opposite has been recommended as well (Chatrath et al. 2008). In this study we could not corroborate an indication for screening of these patients. If a tinnitus-related abnormality was found chances were high (and significant) that the patient had unilateral tinnitus (6/7). The total yield of a routine diagnostic MRI scan was still not high (5%) though in unilateral tinnitus patients. The yield contributory to the diagnosis (two vestibular schwannomas) was even lower (1.7%). Both these patients showed audiometric asymmetry and would thus have been screened on the basis of this indication. None of the patients with unilateral tinnitus and normal hearing included in this study (thirty-seven patients) had a vestibular schwannoma. This is a fairly small and select group of patients though, and it is therefore recommended that the yield of a routine MRI scan in unilateral tinnitus patients with normal hearing should additionally be studied to adequately assess the yield of a routine MRI scan in this population.

There was a high rate of incidental findings (41%) in this study. This is in agreement with previous studies in patients with audiovestibular symptoms (33 – 48%) (Chisholm et al. 2006; Papanikolaou et al. 2010). Although much lower numbers of 1.4% have been reported as well (Vandervelde and Connor 2009). Our most common incidental finding was age-related effects in 16% of patients. This is fairly lower than reported in other studies on MRI scans in patients with audiovestibular symptoms, that mention rates of 22 – 29% (Papanikolaou et al. 2010; Sedwick et al. 2001). The incidence of age-related effects depends on the age of the included patients. Patients in our study had a mean age of 51 years, which was lower than the mean age in one of the studies reporting a higher incidence (59 years) (Sedwick et al. 2001).

The other study does not report a mean age for their study population (Papanikolaou et al. 2010). The vascular anomalies that we often found were not reported in other studies. The most common potential clinical significant incidental finding in this study was an arachnoid cyst in 1.8% of patients. This is in line with reported numbers in other studies of 0.94 – 1.5% (Chisholm et al. 2006; Papanikolaou et al. 2010; Vandervelde and Connor 2009).

In our study a high proportion of type II and III AICA loops was found (in 23% of patients). This is in the lower range of proportions described in other studies of 19-39%, with an average of 30% (Clift et al. 2009; Gorrie et al. 2010; Gultekin et al. 2008; Kanzaki and Ogawa 1988; Makins et al. 1998; McDermott et al. 2003; van der Steenstraten et al. 2007). It has to be noted though that most of these studies count the number of AICA loops, where we counted the number of patients with an AICA loop. Hence in our study bilateral AICA loops were counted only once, compared to twice in most other studies. We could not show a relationship between the presence of an AICA loop and the symptoms of the patient. Most other studies also did not find a relationship between an AICA loop and hearing loss (Clift et al. 2009; Gorrie et al. 2010; Makins et al. 1998; van der Steenstraten et al. 2007) or tinnitus (Gultekin et al. 2008; Makins et al. 1998; McDermott et al. 2003). In contrast, relationships between the presence of an AICA loop and unilateral hearing loss (McDermott et al. 2003), or with idiopathic sudden deafness, idiopathic sensorineural hearing loss or Menière's disease (Kanzaki and Ogawa 1988) have been shown. When looking at the diagnostic criteria for cochleovestibular nerve compression syndrome of the TRI, a definite syndrome was only shown in three patients (4.3%) that had an AICA loop on the MRI scan. This shows that the presence of an AICA loop on an MRI scan is only weakly related to a cochleovestibular nerve compression syndrome and thus the syndrome cannot be concluded from the presence of an AICA loop on the MRI scan. Therefore, an MRI scan should not be performed routinely to exclude this syndrome in patients with tinnitus. An MRI scan to exclude a role of an AICA loop in the etiology of tinnitus should to our feeling only be performed when this syndrome is suspected based on clinical indications.

The most important limitation of our study is that it only includes patients that were seen in a tertiary tinnitus clinic. Patients had generally already been seen by an otorhinolaryngologist or an audiologist in the past and had sometimes undergone different forms of assessment. It is possible that some of these patients had already had an MRI scan previously. This scan would then have been without abnormalities, otherwise the patient would not have been presented to our clinic. It is therefore plausible that there is an underestimation of abnormalities related to tinnitus in our population compared to a population of tinnitus patients that would be scanned at their primary visit. Care should be taken in extrapolating these results to a general tinnitus population, but considering the low number of related abnormalities found in this study, it seems likely that the yield of a routine MRI scan could be low in such a population as well. Considering that almost all

tinnitus-related MRI abnormalities in this study were found in unilateral tinnitus patients, this limitation could play a larger role in the generalization for these patients.

In this study it was shown that a routine MRI scan is of little or no value in tinnitus patients with persistent complaints. It is advised to only perform an MRI scan in bilateral tinnitus patients when on clinical grounds, such as an asymmetrical hearing loss or unilateral neurologic findings, a cause for the tinnitus is expected (e.g. vestibular schwannoma, cochleovestibular nerve compression syndrome). This study shows no evidence that a screening MRI scan should be considered more readily in unilateral tinnitus patients (with normal hearing). Considering that almost all tinnitus-related MRI abnormalities in this study were found in unilateral tinnitus patients, this forms an indication for further research to assess whether a routine MRI scan in unilateral tinnitus patients (with normal hearing) should nevertheless be considered AICA loops are often encountered on an MRI scan, but rarely relate to the tinnitus and should thus be considered incidental findings.

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Chapter 5

Anticonvulsants for Tinnitus

Hoekstra CE, Rynja S, van Zanten BG, Rovers MM., Anticonvulsants for tinnitus, *Cochrane Database syst Rev.* 2011 Jul 6;(7). Review

ABSTRACT

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

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

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

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

Data collection and analysis: Three authors assessed risk of bias and extracted data independently.

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

Conclusions: Current evidence regarding the effectiveness of anticonvulsants in patients with tinnitus has significant risk of bias. There is no evidence from studies performed so far to show that anticonvulsants have a large positive effect in the treatment of tinnitus but a small effect (of dubious clinical significance) has been demonstrated.

INTRODUCTION

Parts of this introduction are partially based on earlier work in the following Cochrane reviews and reproduced with permission (Baldo et al. 2006; Bennett et al. 2007; Hilton and Stuart 2009; Hobson et al. 2010; Phillips and McFerran 2010).

Description of condition

Tinnitus is a phantom auditory perception of meaningless sound in the absence of an external or internal acoustic stimulation. While, for the patient, this perception of noise is very real, it can be considered a phantom, or false, perception because there is no corresponding external sound. For the patient it may be trivial or it may be a debilitating condition (Luxon 1993). The characteristics of the perceived sound (description, number, frequency, onset, presence and location of the sound) can vary enormously between patients. For example, patients may hear a single sound or multiple sounds, it may be perceived in one ear, both ears, within the head or outside the body and the symptom may be continuous or intermittent.

It is important to distinguish between clinically significant and non-significant tinnitus (Davis and Rafaie 2000) and several different classifications have been proposed (Dauman and Tyler 1992; McCombe et al. 2001; Stephens and Hetu 1991). Severe tinnitus, defined as tinnitus interfering with the normal way of life, is reported in up to 5% of tinnitus patients (Coles 1984; Davis and Rafaie 2000; Nondahl et al. 2002). It is usually associated with other symptoms, such as hyperacusis and many of these patients also suffer from affective disorders and sleeping problems (Crummer and Hassan 2004; Henry et al. 2005; Jastreboff and Jastreboff 2003; Moller 2003).

Differentiation between tinnitus and somatosounds (perceptions of sound caused by an internal acoustic source, due to either a vascular abnormality or a muscular or anatomical cause such as sound generated by blood flow in or around the ear or unusual activity of middle ear muscles within the middle ear) is important because they have different pathophysiologies and therefore different therapeutic approaches. Somatosounds are usually objective; they can be detected by an examiner, either unaided or using a listening aid such as a stethoscope or microphone in the ear canal. Somatosounds are much less common than tinnitus. Tinnitus is by definition always subjective, meaning that it cannot be heard by anyone other than the patient, while for the patient this perception of noise is real.

Etiology

The most common causes of tinnitus are otological disorders, most frequently noise and age-induced sensorineural hearing loss, or other types of sensorineural hearing loss. Conductive

hearing loss can also cause tinnitus, sometimes transient. Almost any form of disorder involving the outer, middle or inner ear or the auditory nerve may be associated with tinnitus (Brummett 1980; Shea 1981). However, it is possible to have severe tinnitus with no evidence of any aural pathology. Presumably in these cases there is a moderate degree of aural pathology, but not evident enough to be able to diagnose with current diagnostic methods (audiometry only screens a portion of the auditory function). Non-otological causes of tinnitus have also been described, but the causal relationship is less understood. Conversely, tinnitus can even exist without a peripheral auditory system: when the cochlear nerve is severed patients retain their tinnitus (Baguley et al. 1992). This suggests the fundamental importance of the central auditory pathways in the development or maintenance of the symptom, irrespective of trigger.

Pathophysiology

Over 50 years ago, Heller and Bergman demonstrated that if 'normal' people (with no known cochlear disease) were placed in a quiet enough environment, the vast majority of them would experience sounds inside their head. They concluded that tinnitus-like activity is a natural phenomenon perceived by many in a quiet enough environment (Heller and Bergman 1953).

Despite the high prevalence and morbidity of tinnitus, its pathophysiology is poorly understood. It is probable that different processes are involved in the generation of tinnitus; for example, when it is transient or chronic or when it is caused by conductive or sensorineural hearing loss. Possible theories on the pathophysiology focus on dysfunction of hair cells, the auditory nerve or central auditory system. In the 'neurophysiological model' of tinnitus (Jastreboff 1990; Jastreboff and Hazell 2004) it is proposed that tinnitus results from the abnormal processing of a signal generated in the auditory system. This abnormal processing occurs before the signal is perceived centrally. This may result in 'feedback', whereby the annoyance created by the tinnitus causes the individual to focus increasingly on the noise, which in turn exacerbates the annoyance and so a 'vicious cycle' develops. In this model tinnitus could therefore result from continuous firing of cochlear fibers to the brain, from hyperactivity of cochlear hair cells or from permanent damage to these cells being translated neuronally into a 'phantom' sound-like signal that the brain 'believes' it is hearing.

It is commonly thought that chronic tinnitus (caused by sensorineural hearing loss) is generated in the brain as a result of functional reorganization of the primary auditory cortex, following damage to the peripheral auditory system (Eggermont and Roberts 2004). This functional reorganization would cause the tonotopic maps in the central auditory cortex to alter. This altering of maps has indeed been shown in humans with tinnitus (Muhlnickel et al. 1998). On the neuronal level, it is thought that this functional reorganization causes an increased spontaneous firing rate of neurons in the auditory cortex and auditory brainstem,

and an increased synchronization of spontaneous activity of cortical neurons (Eggermont and Roberts 2004; Norena and Eggermont 2003; Ochi and Eggermont 1997). This increase in firing rate and synchronization would lead to hyperactivity in the central auditory system. This resulting hyperactivity has been shown in functional magnetic resonance imaging (fMRI) research in tinnitus patients (Giraud et al. 1999; Lockwood et al. 1998; Melcher et al. 2000). The mechanism underlying this increase in spontaneous firing rate and synchronization is thought to be reduced inhibition, which is the consequence of the decreased output from damaged cochlear regions (Eggermont and Roberts 2004; Salvi et al. 2000).

The relationship between the symptom of tinnitus and the activity of the prefrontal cortex and limbic system has been emphasized. The limbic system mediates emotions. It can be of great importance in understanding why the sensation of tinnitus is in many cases so distressing for the patient. It also suggests why, when symptoms are severe, tinnitus can be associated with major depression, anxiety and other psychosomatic and/or psychological disturbances, leading to a progressive deterioration of quality of life (Lockwood et al. 1999; Sullivan et al. 1992; Sullivan et al. 1993; Sullivan et al. 1989).

Prevalence

Epidemiological data reports are few. Reports show that tinnitus is common, affecting approximately 7% to 19% of the adult population (Chung et al. 1984; Coles 1984; Davis and Rafaie 2000; Davis 1989; Henry et al. 2005; Nondahl et al. 2002). This substantial variance might be explained by the different definitions and criteria of tinnitus that were used and the different populations that were investigated. The largest single study was undertaken in the UK by the Medical Research Council Institute of Hearing Research and was published in 2000 (Davis and Rafaie 2000). This longitudinal study of hearing questioned 48,313 people; 10.1% described tinnitus arising spontaneously and lasting for five or more minutes at a time and 5% described it as moderately or severely annoying. However, only 0.5% reported tinnitus having a severe effect on their life. This is another of the paradoxes of tinnitus: the symptom is very common but the majority of people who experience it are not particularly concerned by it. These figures from the UK are broadly consistent with data collected by the American Tinnitus Association (ATA) which suggests that tinnitus may be experienced by around 50 million Americans, or 17% of the US population (American Tinnitus Association). Data also exist for Japan, Europe and Australia (Sindhusake et al. 2003), and estimates suggest that tinnitus affects a similar percentage of these populations, with 1% to 2% experiencing debilitating tinnitus (Seidman 1998). Tinnitus can occur at any age, but the prevalence increases with advancing age (peak prevalence between 40 and 70 years) (Baguley and McFerran 1999; Crummer and Hassan 2004; Davis and Rafaie 2000; Hegarthy and Smith 2000; Henry et al. 2005; Schleuning 1991). The Oregon Tinnitus Data Archive (Meikle et al. 1995) contains data on the characteristics of tinnitus drawn from a sample of 1630 tinnitus patients. The age

groups with the greater prevalence are those between 40 and 49 years (23.9%) and between 50 and 59 years (25.6%).

Diagnosis

Firstly a patient with tinnitus may undergo a basic clinical assessment. This will include the relevant otological, general and family history, and an examination focusing on the ears, teeth and neck and scalp musculature. Referral to a specialist is likely to involve a variety of other investigations including audiological tests and radiology. Persistent, unilateral tinnitus may be due to a specific disorder of the auditory pathway and imaging of the cerebellopontine angle is important to exclude, for example, a vestibular schwannoma (acoustic neuroma)- a rare benign tumor of the cochleovestibular nerve. Other lesions, such as glomus tumors, meningiomas, adenomas, vascular lesions or neurovascular conflicts may also be detected by imaging (Marx et al. 1999; Weissman and Hirsch 2000).

Treatment

At present no specific therapy for tinnitus is acknowledged to be satisfactory in all patients. Many patients who complain of tinnitus, and also have a significant hearing impairment, may benefit from a hearing aid (Del Bo and Ambrosetti 2007). Not only will this help their hearing disability but the severity of their tinnitus may be reduced by masking it through the amplification of ambient sounds. Tinnitus masking can also be achieved with devices which produce a sound that can reduce or eliminate the perception of tinnitus (Hobson et al. 2010).

The role of pharmacotherapy in the treatment of tinnitus is still inconclusive. A wide range of drugs have been proposed for the treatment of tinnitus symptoms since it was shown that intravenous lignocaine may be effective in suppressing tinnitus in some patients (Melding et al. 1978). Pharmacological interventions used include cortisone (Koester et al. 2004), vasodilators, benzodiazepines, lidocaine, and spasmolytic drugs. Antidepressants are commonly prescribed for tinnitus. However, two reviews (Baldo et al. 2006; Robinson 2007) have shown that there is no indication that tricyclic antidepressants have a beneficial effect. A Cochrane Review showed that there is no evidence that Ginkgo biloba is effective (Hilton and Stuart 2009).

Psychological therapies (counseling, cognitive behavioral therapy and tinnitus retraining therapy (TRT)) may diminish tinnitus by lessening the distress caused by it or by improving quality of life by teaching coping strategies, relaxation techniques and distraction skills (Andersson and Lyttkens 1999; Martinez-Devesa et al. 2010; Phillips and McFerran 2010). A Cochrane Review has shown that CBT can have an effect on the qualitative aspects of tinnitus and can improve patients' ability to manage the condition (Martinez-Devesa et al. 2010).

Other options for the management of patients with tinnitus which have been evaluated, include music therapy (Argstatter et al. 2008), traditional Chinese medicine, including acupuncture (Li et al. 2009) and hyperbaric oxygen therapy (HBOT). Hyperbaric oxygen therapy (HBOT) can improve oxygen supply to the inner ear which, it is suggested, may result in an improvement in tinnitus, however a Cochrane Review found insufficient evidence to support this (Bennett et al. 2007).

Different treatment modalities working on the assumption that tinnitus is related to central auditory hyperactivity are being evaluated, including transcranial magnetic stimulation (Meng et al. 2011) and extradural electrical stimulation of the auditory cortex (De Ridder et al. 2007).

Anticonvulsants

Anticonvulsants form an important group of drugs used in the treatment of tinnitus. Also because of this assumption that tinnitus is related to central auditory hyperactivity. Different reviews and non randomized controlled trials have been published mentioning anticonvulsants (Dobie 1999; Goodey 1981; Melding and Goodey 1979; Shea and Harell 1978; Waddell 2005). Anticonvulsants might diminish this hyperactivity and treat tinnitus in three ways: 1) they may enhance inhibition in the central auditory system by augmenting the action of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter; 2) they may lower the excitation level in the central auditory system by lessening glutamate transmission, an excitatory neurotransmitter; 3) they may halt the depolarization of cells, and thus central activation, by blocking voltage-dependent sodium channels.

The effectiveness of anticonvulsants in tinnitus patients is, however, not yet clear. A comprehensive systematic review and meta-analysis of randomized controlled trials evaluating the effectiveness of anticonvulsants in patients with chronic tinnitus is therefore warranted.

Objectives

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

METHODS

Types of studies

We considered all randomized controlled trials and cross-over trials (if data could be extracted before the cross-over) in which anticonvulsants were compared with placebo, for inclusion in this review. Desirable time points of outcome assessment were four and eight weeks. Single dose studies were excluded.

Types of participants

Studies on patients with chronic tinnitus were included. We excluded studies on patients with somatosounds (carotid pathology, arteriovenous malformations, high cardiac output, hypertension, aortic murmurs, vascular tumors, atherosclerosis of the subclavian artery, persistent stapedial artery, turbulent stream in the jugular vein, pseudotumour cerebri or myoclonus of the muscles in the palate or within the ear), and patients with auditory hallucinations. Somatosounds were differentiated on the basis of brain imaging or on characteristic features in the history.

Types of interventions

We included studies with orally administered anticonvulsants (without restrictions regarding type of anticonvulsant, dose or frequency) versus placebo.

Primary outcome

- Improvement in tinnitus-specific health-related quality of life measured with validated questionnaires, such as the Tinnitus Questionnaire (TQ), Tinnitus Handicap Inventory (THI), Tinnitus Handicap Questionnaire (THQ) or Tinnitus Experience Questionnaire (TEQ).

Secondary outcomes

- Improvement in self-assessment of tinnitus severity measured with self-assessment scores.
- Improvement in accompanying symptoms, such as depression, anxiety or sleeping problems measured with validated questionnaires such as the Profile of Mood States, Beck Depression Scale, State-Trait Anxiety Inventory or Brief Symptom Inventory.
- Adverse drug effects.

Search methods for identification of studies

We conducted systematic searches for randomized controlled trials on the effectiveness of anticonvulsants in patients with tinnitus. There were no language, publication year or publication status restrictions. The date of the last search was 26 May 2010.

Electronic searches

We searched the following databases from their inception: the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 2); PubMed (1950 onwards); EMBASE (1974 onwards); CINAHL (1982 onwards); PsycINFO; LILACS; KoreaMed; IndMed; PakMediNet; CNKI; MEMR (Index Medicus for WHO Eastern Mediterranean Region); IMSEAR (index Medicus for WHO South-East Asia Region); Hellis Metasearch; J-East (Science Links Japan); UKCRN (the UK Clinical Research Network Portfolio Database); ICTRP (the World Health Organization International Clinical Trials Registry Platform); ClinicalStudyResults.org; *m*RCT (the *meta*Register of Controlled Trials) and Google.

Search strategies

Subject strategies for databases were modeled on the search strategy designed for CENTRAL (see Table 1). Where appropriate, we combined subject strategies with adaptations of the highly sensitive search strategy designed by the Cochrane Collaboration for identifying randomized controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.2, Box 6.4.b. (Handbook 2008).

Searching other resources

We checked the reference lists of identified publications for additional trials. We searched PubMed, TRIPdatabase, NLH ENT & Audiology Specialist Library and Google to retrieve existing systematic reviews possibly relevant to this systematic review, so that we could scan their reference lists for additional trials. We sought abstracts from conference proceedings via the Cochrane Ear, Nose and Throat Disorders Group Trials Register and CENTRAL.

Data collection and analysis

We conducted the review according to the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions 5.0.1*. (Handbook 2008).

Table 1 Search strategy

CENTRAL	PubMed	EMBASE (Ovid)
#1 MeSH descriptor Tinnitus explode all trees #2 tinnit* #3 (#1 OR #2) #4 MeSH descriptor Anticonvulsants explode all trees #5 MeSH descriptor Carbamazepine #6 MeSH descriptor Vigabatrin #7 MeSH descriptor Phenobarbital #8 MeSH descriptor Ethosuximide #9 MeSH descriptor Clonazepam #10 anticonvul* OR antiepilept* OR anti-epilept* #11 zonisamide OR AD 810 OR CI 912 OR zonegran OR carbamazepine OR Finlepsin OR Neurotol OR Epitol OR amizepine OR Tegretol OR vigabatrin OR gamma Vinyl OR sabri #12 oxcarbazepine OR GP 47680 OR timox OR trileptal OR Phenobarbital OR phenemal OR phenorbarbitone OR Phenylbarbital OR phenylethylbarbituric acid OR gardenal OR luminal OR methsuximide OR mesuximide #13 N,2-dimethyl-2-phenylsuccinimide OR celontin OR petinutin OR lamotrigine OR lamictal OR lamiktal OR gabapentin OR neurontin OR felbamate OR felbatol OR taloxa OR W-554 #14 etiracetam OR levetiracetam OR Keppra OR Emeside OR suksilep OR suxilep OR zarontin OR clonazepam OR antelepsin OR rivotril OR Ro 5-4023 OR clobazam OR frisium OR urbanyl #15 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 #16 #3 AND #15	#1 Tinnitus [Mesh] #2 tinnit* [tiab] #3 #1 OR #2 #4 Anticonvulsants [Mesh] #5 Carbamazepine [MeSH] #6 Vigabatrin [MeSH] #7 Phenobarbital [MeSH] #8 Ethosuximide [MeSH] #9 Clonazepam [MeSH] #10 Clobazam [Substance Name] #11 Etiracetam [Substance Name] #12 Felbamate [Substance Name] #13 Gabapentin [Substance Name] #14 Lamotrigine [Substance Name] #15 Methsuximide [Substance Name] #16 Oxcarbazepine [Substance Name] #17 Zonisamide [Substance Name] #18 Anticonvulsants[Pharmacological Action] #19 etiracetam[tiab] OR levetiracetam[tiab] OR Keppra[tiab] OR Emeside[tiab] OR suksilep[tiab] OR suxilep[tiab] OR zarontin[tiab] OR clonazepam[tiab] OR antelepsin[tiab] OR rivotril[tiab] OR Ro 5-4023[tiab] OR clobazam[tiab] OR frisium[tiab] OR urbanyl [tiab] #20 N,2-dimethyl-2-phenylsuccinimide[tiab] OR celontin[tiab] OR petinutin[tiab] OR lamotrigine[tiab] OR lamictal[tiab] OR lamiktal[tiab] OR gabapentin[tiab] OR neurontin[tiab] OR felbamate[tiab] OR felbatol[tiab] OR taloxa[tiab] OR W-554 #21 oxcarbazepine[tiab] OR GP 47680[tiab] OR timox[tiab] OR trileptal[tiab] OR phenobarbital[tiab] OR phenemal[tiab] OR phenorbarbitone[tiab] OR phenylbarbital[tiab] OR phenylethylbarbituric acid[tiab] OR gardenal[tiab] OR luminal[tiab] OR methsuximide[tiab] OR mesuximide #22 zonisamide[tiab] OR AD 810[tiab] OR CI 912 [tiab] OR zonegran[tiab] OR carbamazepine[tiab] OR finlepsin[tiab] OR neurotol[tiab] OR epitol[tiab] OR amizepine[tiab] OR tegretol[tiab] OR vigabatrin[tiab] OR "gamma vinyl"[tiab] OR sabri #23 anticonvul*[tiab] OR antiepilept*[tiab] OR anti-epilept* [tiab] #24 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 #25 #3 AND #24	1. exp tinnitus/ 2. tinnit*.tw. 3. 1 or 2 4. exp anticonvulsive agent/ 5. exp anticonvulsant activity/ 6. exp anticonvulsant therapy/ 7. (anticonvul* OR antiepilept* OR anti-epilept*).tw. 8. (zonisamide OR AD 810 OR CI 912 OR zonegran OR carbamazepine OR Finlepsin OR Neurotol OR Epitol OR amizepine OR Tegretol OR vigabatrin OR gamma Vinyl OR sabri).tw. 9. (oxcarbazepine OR GP 47680 OR timox OR trileptal OR Phenobarbital OR phenemal OR phenorbarbitone OR Phenylbarbital OR phenylethylbarbituric acid OR gardenal OR luminal OR methsuximide OR mesuximide).tw. 10. N,2-dimethyl-2-phenylsuccinimide OR celontin OR petinutin OR lamotrigine OR lamictal OR lamiktal OR gabapentin OR neurontin OR felbamate OR felbatol OR taloxa OR W-554).tw. 11. (etiracetam OR levetiracetam OR Keppra OR Emeside OR suksilep OR suxilep OR zarontin OR clonazepam OR antelepsin OR rivotril OR Ro 5-4023 OR clobazam OR Frisium OR urbany).tw. 12. 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 13. 3 AND 12

Selection of studies

Two review authors (CELH and SPR) scanned the retrieved abstracts to identify relevant randomized controlled trials. The same two authors reviewed the full texts of these articles. We assessed the eligibility of the trials independently. We resolved any differences in opinion by discussion.

Data extraction and management

Three authors (CELH, SPR and MMR) independently collected and extracted data. Disagreement was resolved by discussion. We extracted the following data from each study: number of included patients, inclusion and exclusion criteria, intervention and placebo

information, trial duration, primary and secondary outcomes, follow up and adverse events. We contacted the original authors for clarification and further data if trial reports were unclear. Where necessary we arranged translations of papers.

Assessment of risk of bias in included studies

We assessed the quality of the included studies using the Cochrane Collaboration's tool for assessing risk of bias ('Risk of bias' table, *Cochrane Handbook for Systematic Reviews of Interventions,* chapter 8 (Handbook 2008). We addressed six specific domains, i.e. sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and 'other biases'. By answering pre-specified questions we judged the risk of bias for each domain as 'yes' (low risk of bias), 'no' (high risk of bias) or 'unclear'. We resolved disagreement by discussion (CELH, SPR and MMR). We planned to assess publication bias with a scatter plot (funnel plot) of the log rate ratios (x-axis) versus precision defined as 1/ standard error (y-axis) (Handbook 2008).

Assessment of heterogeneity

If heterogeneity was low (I^2 < 25%) we calculated the summary weighted risk differences and 95% confidence intervals (CIs) (random-effects model) by the Mantel-Haenszel method, which weighs studies by the number of events in the control group, using the Cochrane statistical package in RevMan (version 5.0) (RevMan 2008).

Data synthesis

We used RevMan 5.0 to carry out the meta-analyses for comparable trials and outcomes. For continuous outcomes (questionnaire scores) we calculated standardized mean differences (SMD) and their corresponding 95% confidence intervals (CI). Standardized mean differences were calculated by dividing the difference between means by the standard deviation. For dichotomous outcomes, we measured the estimates of effect as risk differences (RD) with their corresponding 95% confidence intervals. We calculated risk differences using: (proportion of patients with improvement in intervention group)- (proportion of patients with improvement in placebo group). Furthermore, we also planned to perform sensitivity analyses excluding the studies with the lowest methodological quality, according to the Cochrane Collaboration's risk of bias assessment, to establish whether this factor influences the final outcome. We also intended to perform subgroup analyses for cause of tinnitus, duration of tinnitus, patient age, type of anticonvulsant used and outcome measures used. Ultimately it was not possible to perform sensitivity and subgroup analysis, mainly because of lack of data concerning these factors in the original articles.

RESULTS: DESCRIPTION OF STUDIES

Results of the search

We found 96 studies through the combined searches. First, we sifted the articles by title/ abstract, leaving 15 articles to read in full text. We excluded eight publications from the review (see Table 2). Five articles (Bauer and Brozoski 2006; Guth et al. 1990; Marks et al. 1981; Menkes and Larson 1998; Shulman 2008) did not fit the criteria for this review (no anticonvulsant, non-RCT, comments) and three articles (Castagno 1989; Halmos et al. 1982; Viada et al. 1981) were not available through the databases that we used or through the internet. We identified no additional trials by checking the bibliographies of the selected trials.

Table 2 Characteristics of excluded studies

Study	Reason for exclusion
Bauer 2006	Not randomized (cross-over trial with a set regiment)
Castagno 1989	Not available
Guth 1990	Amino-oxyacetic acid (AOAA) is not a registered anticonvulsant
Halmos 1982	Not available
Marks 1981	Single dose study
Menkes 1998	Article is a letter to the editor and not a randomized controlled trial
Shulman 2008	Article is a comment and not a randomized controlled trial
Viada 1981	Not available

Included studies

We included seven trials (453 patients) that looked at the effectiveness of anticonvulsants in patients with tinnitus in this review (see Table 3-9) (Bakhshaee et al. 2008; Donaldson 1981; Hulshof and Vermeij 1985; Hulshof and Vermeij 1986; Piccirillo et al. 2007; Simpson et al. 1999; Witsell et al. 2007).

Design

Five trials had a randomized controlled trial design (Bakhshaee et al. 2008; Hulshof and Vermeij 1985; Hulshof and Vermeij 1986; Piccirillo et al. 2007; Witsell et al. 2007). The other two studies were cross-over trials (Donaldson 1981; Simpson et al. 1999).

Table 3a Characteristics Bakhshaee 2008

Characteristic	Description
Methods	Prospective, double-blind, placebo-controlled, cross-over trial
Participants	30 participants with moderate to severe idiopathic subjective tinnitus 16 gabapentin, 14 placebo Inclusion criteria • 36 to 81 years • continuous non-pulsatile tinnitus • duration at least 6 months • total Tinnitus Exclusion criteria • active Menière's disease • signs or symptoms of intracranial disease or vestibular disorder • conductive hearing loss or surgically correctable component • sensorineural hearing loss of well-known etiology, such as noise-induced hearing loss • totally deaf or more than moderately severe loss (> 50) in at least one frequency • concurrent treatment with centrally-acting medication • diabetes mellitus • related to gabapentin use (impaired renal function, (planned) pregnancy, contraindications to gabapentin, metabolic or endocrine disorder) • mental retardation and severe cognitive disorders
Interventions	Intervention: 900 mg gabapentin per day Control: identical placebo (opaque starch-filled gel capsules) Duration: 4 weeks
Outcomes	Primary psychoacoustically determined tinnitus loudness and TQ score Secondary outcome: Tinnitus Severity Index score
Notes	Drawbacks • Exclusion criteria result in an intervention group not representative of the majority of tinnitus patients (patients with sensorineural hearing loss of well-known etiology such as noise induced hearing loss are excluded) Adverse events: 3% experienced dizziness

Table 3b Risk of bias Bakhshaee 2008

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	This study is described as a RCT and the results show an intervention and a placebo group. The methods section, however, describes every participant receiving the same treatment sequence and serving as their own control. This implies a cross-over design. As everybody received the same treatment sequence we believe that randomization was not performed.
Allocation concealment (selection bias)	High risk	Everybody received the same treatment sequence
Blinding (performance and detection bias)	Unclear risk	Blinding not adequately described • Identical pills suggests blinding of patients • Same treatment sequence makes blinding of study personnel and outcome assessors doubtful
Incomplete outcome data (attrition bias)	High risk	Not adequately described; 59% drop-out is implied (not included in the analysis)
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Unclear risk	No adequate baseline table to check comparability of groups Not described if groups were treated equally

Table 4a Characteristics Donaldson 1981

Characteristic	Description
Methods	Placebo-controlled, randomized, cross-over trial
Participants	78 tinnitus clinic patients 62 carbamazepine, 62 placebo (patients who dropped out not included) Inclusion criteria: • tinnitus • sensorineural hearing loss Exclusion criteria: • conductive hearing loss • deafness
Interventions	Intervention: 100 mg carbamazepine twice a day Control: placebo tablets Duration: 2 times 2 months
Outcomes	Patients' assessment of tinnitus' change on a percentage (not fully described, presumably 0-100%) analogue scale: excellent (abolition); good (> 60% reduction); partial (30% to 60% reduction); no significant relief (< 30% reduction)
Notes	Adverse events: types not described 18% withdrew because of side effects from carbamazepine and 3% withdrew because of side effects from placebo

Table 4b Risk of bias Donaldson 1981

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization process not explained
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance and detection bias)	High risk	Blinding is not explained. The study date and the fact that no study pharmacy is mentioned mean that adequate blinding is judged highly unlikely.
Incomplete outcome data (attrition bias)	High risk	21% drop-out (18% intervention, 3% placebo) is too high and patients that dropped out were excluded from analyses
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Unclear risk	No adequate baseline table to check comparability of groups Not described if groups were treated equally

Table 5a Characteristics Hulshof 1985

Characteristic	Description
Methods	Double-blind, placebo-controlled, randomized trial
Participants	48 patients with annoying tinnitus 24 carbamazepine, 24 placebo No further inclusion/exclusion criteria described
Interventions	Intervention: 150 mg carbamazepine three times a day Control: identical-looking gelatin placebo capsules Duration: 30 days
Outcomes	Likert scale (tinnitus disappeared, tinnitus improved, tinnitus did not disappear)
Notes	Adverse events: 63% of carbamazepine patients experienced side effects (8 dizziness, 8 nausea, 4 headache, 2 tiredness, 2 vomiting, 1 diarrhea). 4% of placebo patients experienced side effects (1 headache).

Table 5b Risk of bias Hulshof 1985

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization process not explained
Allocation concealment (selection bias)	Unclear risk	Randomization process not explained
Blinding (performance and detection bias)	Unclear risk	Blinding not adequately described • Identical pills suggest at least blinding of patients • Measurements of carbamazepine levels in serum makes blinding of personnel doubtful
Incomplete outcome data (attrition bias)	High risk	42% drop-out in the intervention group is very high; patients were included in analyses
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Unclear risk	No adequate baseline table to check comparability of groups Not described if groups were treated equally

Table 6a Characteristics Hulshof 1986

Characteristic	Description
Methods	Double-blind, placebo-controlled, randomized trial
Participants	50 patients with annoying tinnitus 25 flunarizine, 25 placebo No further inclusion/exclusion criteria described
Interventions	Intervention: 10 mg flunarizine once a day Control: identical placebo capsules Duration: 6 weeks
Outcomes	Likert scale (0 tinnitus has disappeared, 1 tinnitus persists but is no longer annoying, 2 tinnitus annoying but less severe, 3 no change, 4 severity increased)
Notes	Adverse events: 8% of flunarizine patients experienced sleepiness during the day. No side effects were mentioned in the placebo group.

Table 6b Risk of bias Hulshof 1986

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization process not explained
Allocation concealment (selection bias)	Unclear risk	Randomization process not explained
Blinding (performance and detection bias)	Unclear risk	Blinding process not adequately described • Identical pills suggest at least blinding of patients • Measurement of flunarizine levels in serum makes blinding of personnel doubtful
Incomplete outcome data (attrition bias)	Unclear risk	Not adequately described if there were no drop-outs, or if the 50 patients analyzed were the patients left over after exclusion of a number of drop-outs
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Unclear risk	No adequate baseline table to check comparability of groups Not described if groups were treated equally

Table 7a Characteristics Piccirillo 2007

Characteristic	Description
Methods	Double-blind, placebo-controlled, randomized trial
Participants	135 subjects with severe idiopathic subjective tinnitus (1028 screened) 59 gabapentin, 56 placebo Inclusion criteria: • 18 to 65 years • duration of 6 months or longer • sufficient severity to disrupt daily activities • Tinnitus Handicap Inventory (THI) $\geq$ 38 Exclusion criteria: • presence of a treatable otological disorder related to the tinnitus • organic mental disorder related to gabapentin use (impaired renal function, previous use of gabapentin)
Interventions	Intervention: 3600 mg gabapentin per day in 3 doses or highest possible dose reached (titration: week 1, 900 mg/d; week 2, 1800 mg/d; week 3, 2700 mg/d; week 4, 3600 mg/d) Control: identical blue placebo capsule, similar administration Duration: 4 weeks titration period and 4-week fixed-dose period
Outcomes	Primary outcome: change in THI from week 0 to 8 between treatment arms Secondary outcomes: 1) Patient Global Impression of Change score, 2) Brief Symptom Inventory, 3) Beck Depression Scale score
Notes	Drawbacks: • Some results difficult to interpret from tables because of different subgroups in baseline and results tables • Unclear why slightly more patients received gabapentin than placebo Adverse events: 7% withdrew because of side effects (3 nausea, 2 weight gain, 2 sleep disturbance, 2 dizziness, 1 seizure). It was not mentioned if the side effects occurred in the gabapentin or the placebo group.

Table 7b Risk of bias Piccirillo 2007

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate randomization process (sequentially randomized according to a computer-generated random code)
Allocation concealment (selection bias)	Low risk	Adequate concealment (research pharmacist maintained the randomization schedule)
Blinding (performance and detection bias)	Low risk	Double blind, adequate matching placebo capsules
Incomplete outcome data (attrition bias)	Low risk	16% drop out in gabapentin group and 14% in placebo group Modified intention-to-treat analyses (inclusion of patients with at least 1 dose of study medication and at least 1 follow-up assessment)
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Low risk	-

Table 8a Characteristics Simpson 1999

Characteristic	Description
Methods	Double-blind, placebo-controlled, cross-over trial
Participants	33 subjects from a general tinnitus clinic population No other inclusion criteria mentioned Exclusion criteria • younger than 18 or older than 75 years • related to lamotrigine use (pregnancy, (history of) treatment for epilepsy or treatment with antiepileptic drugs, history of gastrointestinal hepatic or renal insufficiency) • < 5 on visual analogue scale (VAS) of 1 to 10 for "annoyance" tinnitus at present level for less than 6 months
Interventions	Intervention: 100 mg/d lamotrigine (titration: week 1 to 2, 25 mg/d; week 3 to 4, 50 mg/d) Control: matching placebo tablets Duration: 4 weeks titration period, 4 weeks fixed-dose period, followed by same regimen after cross-over
Outcomes	Questionnaires (Likert: much better, better, no change, worse, much worse), visual analogue scales (loudness, annoyance, awareness) and audiological measurements (pure tone audiometry, masking audiogram, pitch matching of tinnitus, loudness matching of tinnitus, masking of tinnitus, residual inhibition and uncomfortable loudness levels) at 0 weeks, 4 weeks, 8 weeks, 12 weeks and 16 weeks
Notes	Drawbacks: • No primary outcome measurement or time point stated • No wash-out period Adverse events: 3% of patients withdrew in the lamotrigine group (1 nausea, vomiting and headache) and 3% of patients withdrew in the placebo group (1 dizziness and rash).

Table 8b Risk of bias Simpson 1999

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization process not explained
Allocation concealment (selection bias)	Unclear risk	Randomization process not explained
Blinding (performance and detection bias)	Unclear risk	Blinding process not adequately described. Identical pills suggest at least blinding of patients.
Incomplete outcome data (attrition bias)	Low risk	6% drop-out, evenly distributed in placebo and lamotrigine group Left out from results
Selective reporting (reporting bias)	Unclear risk	No protocol available No primary outcome measurement or time point stated
Other bias	Unclear risk	No adequate baseline table to check comparability of groups Not described if groups were treated equally

Table 9a Characteristics Witsell 2007

Characteristic	Description
Methods	Double-blind, placebo-controlled, randomized clinical trial
Participants	79 patients with moderate tinnitus (102 screened) 53 gabapentin, 26 placebo Inclusion criteria: • 18 to 70 years • chief complaint of tinnitus > 3 months • understands English and has a telephone Exclusion criteria: • related to gabapentin use (allergic to gabapentin, history of chronic renal failure, pancreatitis, hypotension, seizure disorder, past use of gabapentin, pregnant or breast feeding) • cognitive impairment
Interventions	Intervention: 1800 mg gabapentin per day in 3 doses Control: identical placebo capsules in same dosing schedule Duration: 2 week escalating-dose period (week 1, 300 mg/day; week 2, 900 mg/day), 2 week fixed-dose period, 2 weeks descending-dose period (week 5, 900 mg/day; week 6, 300mg/day)
Outcomes	Primary outcome: Tinnitus Handicap Inventory (THI), no time period stated (questionnaire was administered at week 1, week 4, week 10) Secondary outcome: Profile of Mood States (POMS)
Notes	Adverse events: 2% of patients in the gabapentin group experienced side effects (1 mouth sores and decreased libido)

Table 9b Risk of bias Witsell 2007

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate randomization process (computerized random-number generator)
Allocation concealment (selection bias)	Low risk	Adequate concealment (key to randomization was held by the pharmacy)
Blinding (performance and detection bias)	Low risk	Double blind, adequate identical placebo capsules
Incomplete outcome data (attrition bias)	High risk	30% drop-out, selective loss to follow up Unclear handling of drop-out
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Unclear risk	No adequate baseline table to check comparability of groups Not described if groups were treated equally

Sample size

The average sample size was 62 patients (range 9 to 135 patients).

Settings

Some studies did not describe their settings (Bakhshaee et al. 2008; Hulshof and Vermeij 1985; Piccirillo et al. 2007). The other studies described their settings only broadly. Two studies were performed in a tinnitus clinic population (Donaldson 1981; Simpson et al. 1999). One study included patients from a regular otorhinolaryngology practice and also through public advertisement (Witsell et al. 2007). Another study mentions only that outpatients were included (Hulshof and Vermeij 1986).

Participants

Participant characteristics and inclusion and exclusion criteria were not reported in great detail in most studies. Four studies mentioned the age groups that were included, ranging from 18 to 81 years (Bakhshaee et al. 2008; Piccirillo et al. 2007; Simpson et al. 1999; Witsell et al. 2007). Four studies gave information on the duration of the tinnitus. Three studies included patients with tinnitus present at the same level at enrolment for more than the preceding six months (Bakhshaee et al. 2008; Piccirillo et al. 2007; Simpson et al. 1999) and one study included patients with tinnitus for more than three months (Witsell et al. 2007). One study described the character of the tinnitus, which needed to be continuous and non-pulsatile (Bakhshaee et al. 2008). Five studies applied restrictions on the degree of tinnitus. Three studies used a broad description as "annoying tinnitus" (Hulshof and Vermeij 1985; Hulshof and Vermeij 1986) or "sufficient severity to disrupt daily activities" (Piccirillo et al. 2007). Two studies used a minimal score on a questionnaire or visual analogue scale; >38 on the THI (Piccirillo et al. 2007), >30 on the TQ (Bakhshaee et al. 2008m), or >5 on a visual analogue scale (VAS) of 0-10 (Simpson et al. 1999).

The exclusion criteria most often mentioned were related to the anticonvulsants used (Bakhshaee et al. 2008; Piccirillo et al. 2007; Simpson et al. 1999; Witsell et al. 2007). Two studies restricted patients on their hearing level. One included only patients with a sensorineural hearing loss but patients with deafness were excluded (a definition for deafness was not given) (Donaldson 1981). The other study did not include patients with Menière's disease, conductive hearing loss, sensorineural hearing loss of "well-known etiology", or more than moderately severe loss (> 50 (no units given)) in at least one frequency (Bakhshaee et al. 2008). The exclusion criterion "sensorineural hearing loss of well-known etiology" includes noise induced hearing loss, but is not explained any further. Three studies excluded participants with cognitive disorders or impairment (Bakhshaee et al. 2008; Piccirillo et al. 2007; Witsell et al. 2007).

Baseline patient characteristics were often not reported, precluding any judgments about the comparability of the patient groups both within and between trials.

Interventions

These studies investigated four different anticonvulsants. Gabapentin was the drug of investigation in three trials in different dosages and duration (four weeks 900 mg per day; four weeks 1800 mg per day; eight weeks 3600 mg per day) (Bakhshaee et al. 2008; Piccirillo et al. 2007; Witsell et al. 2007). Two studies looked at carbamazepine in different dosages and durations (eight weeks 200 mg; four weeks 450 mg) (Donaldson 1981; Hulshof and Vermeij 1985). Lamotrigine and flunarizine were both studied in one trial (Hulshof and Vermeij 1986; Simpson et al. 1999). All studies were placebo-controlled.

None of the studies included another form of treatment during the study period (such as counseling for example). All studies had one or more evaluation moments. None of the studies described in detail how or by whom the evaluation was performed and if there was any form of interaction between the clinician and the patients during the study.

Outcomes

Three studies used a validated questionnaire as outcome measurement (our primary outcome measure); the Tinnitus Handicap Inventory (THI) was used in two trials (Piccirillo et al. 2007; Witsell et al. 2007) and the Tinnitus Questionnaire (TQ) in one (Bakhshaee et al. 2008). Four studies used different Likert scales as outcome measurement (our secondary outcome measure) (Donaldson 1981; Hulshof and Vermeij 1985; Hulshof and Vermeij 1986; Simpson et al. 1999).

RESULTS: RISK OF BIAS IN INCLUDED STUDIES

Figure 1 and Figure 2 show the results of the risk of bias assessment according to the Cochrane Collaboration's tool for assessing risk of bias. Figure 1 shows the judgments about each methodological quality item presented as percentages across included studies, whereas Figure 2 shows the judgment for each included study separately. Detailed information about the assessment can be found in the Characteristics of included studies. In summary, the overall risk of bias of the included studies is 'high' or 'unclear'.

Bakhshaee 2008 (gabapentin): This appears to be a cross-over trial for which the randomization procedure and treatment protocol are not described clearly. It therefore scored low for sequence generation, allocation concealment and blinding. The drop-out rate was high (59%) and these incomplete outcome data are not addressed. Tinnitus patients with a sensorineural hearing loss of well-known etiology were excluded. This exclusion criterion is not described sufficiently, but it is stated to include noise-induced hearing loss. As this is one of the main causes of hearing loss and consequently tinnitus this will decrease the generalisability of this study.

Donaldson 1981 (carbamazepine): This appears to be a single-blind trial and therefore scored low for blinding. The drop-out rate is high (21%) and these incomplete outcome data are not addressed. The other items were not reported clearly in the paper.

Hulshof 1985 (carbamazepine): The drop-out rate in the intervention group is high (41%), and these incomplete data are not addressed. The other items were not reported clearly in the paper.

Hulshof 1986 (flunarizine): Due to incomplete reporting none of the items to assess the risk of bias could be scored.

Piccirillo 2007 (gabapentin): All items were reported and methodologically sound (i.e. low risk of bias).

Simpson 1999 (lamotrigine): Blinding appears to have been carried out correctly as identical capsules were used for placebo. The other items were not adequately reported and therefore could not be assessed.

Witsell 2007 (gabapentin): The randomization process, allocation concealment and blinding are all reported and methodologically sound (i.e. low risk of bias for these domains). The drop-out rate was high (30%), however, and selective loss to follow up cannot be precluded.

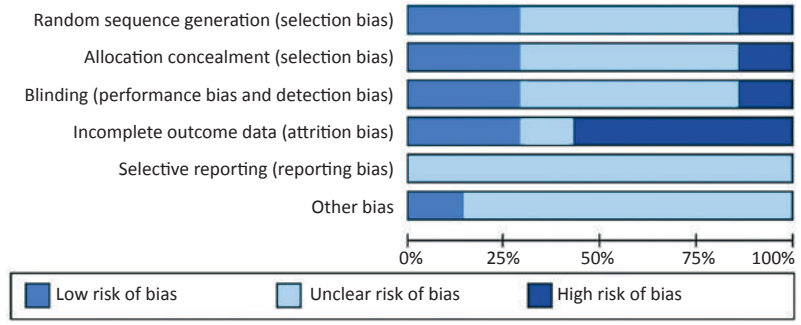

Figure 1 Risk of bias graph: judgments about each methodological quality item presented as percentages across all included studies.

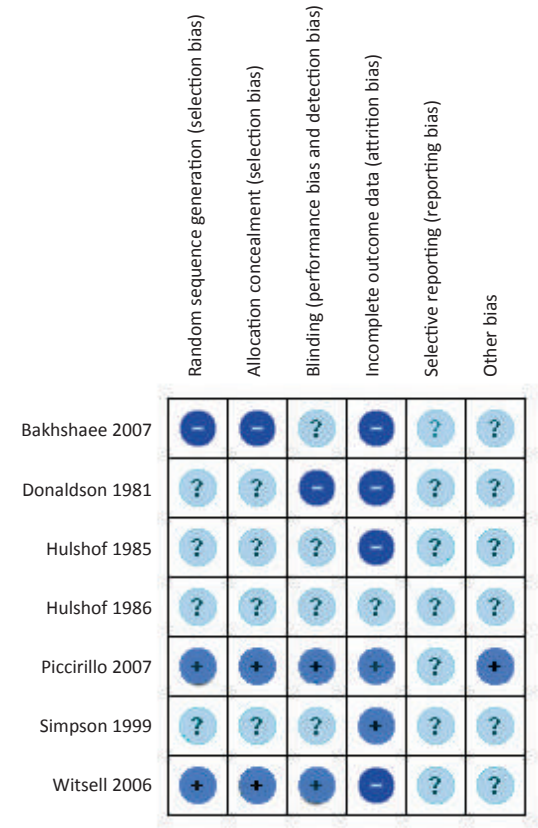

Figure 2 Risk of bias summary: judgments about each methodological quality item for each included study.

RESULTS: EFFECTS OF INTERVENTIONS

Improvement in tinnitus-specific health-related quality of life

The studies included in this review did not show a positive effect of anticonvulsants on the primary outcome. Only three studies, all on gabapentin, evaluated the effect through a validated questionnaire (Bakhshaee et al. 2008; Piccirillo et al. 2007; Witsell et al. 2007). One study showed a negative effect of gabapentin, one study showed a small, statistically non-significant, positive effect and the third study showed no difference between gabapentin and placebo. The data of the studies cannot be pooled as Bakhshaee 2008 used the TQ as outcome measure, Piccirillo 2007 used the THI, and Witsell 2007 did not include exact numbers.

Results for Bakhshaee 2008 and Piccirillo 2007 are shown in table 10. Bakhshaee 2008 showed that treatment with gabapentin for four weeks at 900 mg/d resulted in a negative effect of gabapentin compared to placebo with an increase in TQ score of 18.4 points (standardized mean difference (SMD) 0.82, 95% CI 0.07 to 1.58). This standard mean difference is low because of high standard deviations (20.22 and 23.36, with a total possible score of 84). Piccirillo 2007 showed that treatment with gabapentin for eight weeks at 900 to 3600 mg/d resulted in a positive, non-significant effect for gabapentin with a difference compared to placebo of 2.4 points on the THI (SMD -0.11, 95% CI -0.48 to 0.25) (see table 10). The data in this study included high standard deviations as well (23.52 and 19.02, with a total possible score of 100). In a subgroup of patients with normal hearing the THI improved significantly more in the gabapentin group than in the placebo group (difference 17.2 points, SMD 0.89, 95% CI-1.27 to-0.50). Witsell 2007 showed no differences on the THI after a four-week treatment with gabapentin up to 1800 mg compared to placebo (exact numbers could not be extracted from the article).

Table 10 Outcomes for gabapentin treatment measured on tinnitus-specific questionnaires

Outcome or subgroup	Studies	Participants	Effect estimate Std. Mean Difference (95% CI)
Tinnitus Handicap Inventory (THI)	1	115	-0.11 (-048 – 0.25)
Tinnitus Questionnaire (TQ)	1	30	0.82 (0.07 – 1.58)

Table 11 Pooled outcomes for anticonvulsant treatment measured on self-assessment scales

Outcome or subgroup	Studies	Participants	Effect estimate Std. Mean Difference (95% CI)
Any positive effect	6	445	0.14 (0.06 – 0.22)
Near or total eradication of tinnitus annoyance	6	379	0.04 (-0.02 – 0.11)

Improvement in self-assessment of tinnitus severity

The patient's self-assessment of their tinnitus, our secondary outcome, was included in all studies as an outcome measurement. Outcomes are pooled for the outcomes "any positive effect" and "for near or total eradication of tinnitus annoyance" (see Table 11). Five out of six studies did not show any positive effect of anticonvulsants (Bakhshaee et al. 2008; Donaldson 1981; Hulshof and Vermeij 1986; Piccirillo et al. 2007; Simpson et al. 1999; Witsell et al. 2007). When these data are pooled in a meta-analysis, however, this shows a small favorable effect of anticonvulsants (risk difference (RD) 14%, 95% CI 6% to 22%). This meta-analysis includes all levels of improvement on the various Likert scale, and therefore these patients may still be annoyed to some or a large degree by their tinnitus. It can be presumed that the best possible scores on these Likert scales (complete effect, abolition, not annoying, not annoying/disappeared, very much better, much better) entail annulment of annoyance. Summarized as near or total eradication of tinnitus annoyance, a meta-analysis of these results showed no effect of anticonvulsants (RD 4%, 95% CI -2% to 11%) (Bakhshaee et al. 2008; Donaldson 1981; Hulshof and Vermeij 1985; Hulshof and Vermeij 1986; Piccirillo et al. 2007; Simpson et al. 1999). Figure 3 and Figure 4 show the results of these meta-analyses.

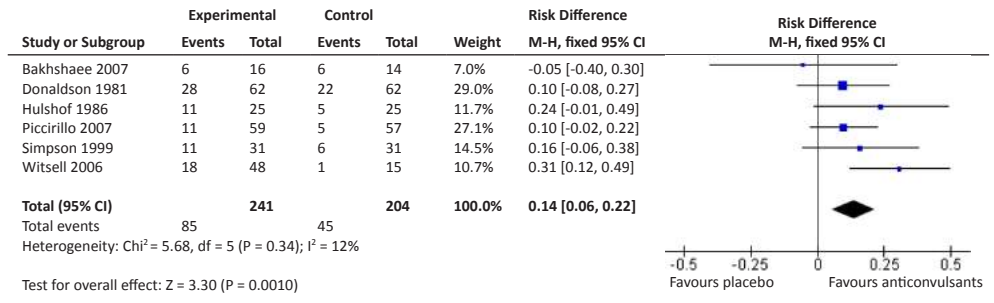

Figure 3 Forest plot of comparison of self-assessment for "any positive effect"

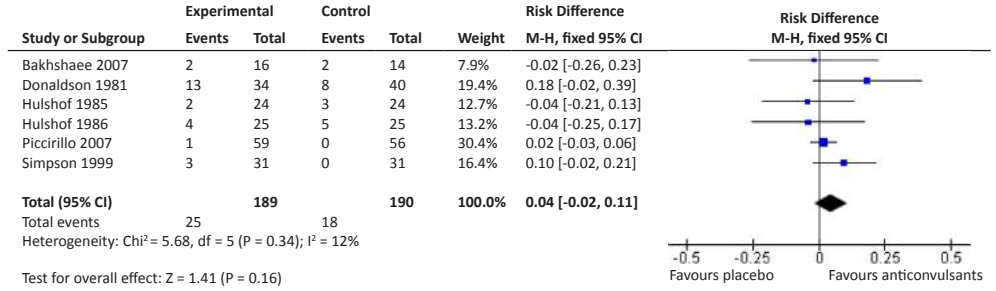

Figure 4 Forest plot of comparison of self-assessment "near or total eradication of tinnitus annoyance"

Gabapentin

Bakhshaee 2008 showed no effect of gabapentin on a self-assessment score (RD 5%, 95% CI -40% to 30%). Complete response was achieved on this score in 13% in the gabapentin group and in 14% of the placebo group (RD 2%, 95% CI-26% to 23%).

Piccirillo 2007 reported a non significant improvement in 19% in the gabapentin group compared to 9% in the placebo group (RD 10%, 95% CI-2% to 22%) on a self-assessment score. A large result was achieved in 2% in the gabapentin group and not in the placebo group (RD 2%, 95% CI-3% to 6%). This difference is also not significant.

Witsell 2007 found a significant effect for gabapentin using a self-assessment score: 38% of patients in the gabapentin group reported a positive effect compared to 7% of placebo patients (RD 30%, 95% CI 14% to 48%).

Carbamazepine

Donaldson 1981 showed that treatment with carbamazepine 200 mg twice a day for two months resulted in a non significant positive effect in 45% as compared to 21% in the placebo group on a self-assessment score (RD 10%, 95% CI-8% to 27%). A good or excellent result was achieved in 38% in the carbamazepine group and in 20% of the placebo group (RD 18%, 95% CI-2% to 39%).

Hulshof 1985 showed that treatment with carbamazepine 150 mg three times a day for 30 days resulted in non significant negative effect : in 8% as compared to 13% in the placebo group on a self-assessment score (RD-4%, 95% CI-21% to 13%).

Flunarizine

Hulshof 1986 showed that treatment with 10 mg flunarizine for six weeks resulted in a non significant improvement of tinnitus in 44% as compared to 24% in the placebo group using a self-assessment score (RD 20%, 95% CI -6% to 46%). Disappearance of the annoyance of tinnitus was not significantly lower in the flunarizine group; 16% in the flunarizine group compared to 20% in the placebo group (RD-4%, 95% CI-25% to 17%)

Lamotrigine

Simpson 1999 showed that treatment with lamotrigine up to 100 mg for eight weeks resulted in a non significant improvement in tinnitus in 36% as compared to 19% in the placebo group using a self-assessment score (RD 16%, 95% CI-6% to 38%). A large improvement was found in 10% of the lamotrigine group and not found in placebo group (RD 10%, 95% CI-2% to 21%). This difference is also not significant.

Improvement in accompanying symptoms (e.g. depression, anxiety or sleeping problems)

Only two studies included outcome measurements on accompanying symptoms. Witsell et al did not find a significant difference in the total mood score of the Profile of Mood States (exact numbers could not be extracted from the article) between the gabapentin and the placebo group (Witsell 2006). Piccirillo et al included the Beck Depression Scale and Brief Symptom Inventory in their analysis, but did not include a description of these data in their article (Piccirillo 2007).

Adverse drug effects

In all studies side effects were reported. Fifty-two of the 286 patients (18%) that received an anticonvulsant experienced side effects. Nausea (12 patients) and dizziness (11 patients) were the most frequently reported. Other side effects reported were: headache (five patients), elevated tiredness (four patients), vomiting during the treatment (three patients), weight gain (two patients), sleep disturbance (two patients), and diarrhea, mouth sores and decreased libido (one patient). In 14 patients the side effects were not specified.

DISCUSSION

Summary of main results

This review of seven trials (453 patients) shows that current evidence regarding the effectiveness of anticonvulsants has a significant risk of bias. Nevertheless, based on the findings in this review anticonvulsants do not show a beneficial effect on tinnitus, measured through validated questionnaires. The seven included trials investigated four different anticonvulsants: gabapentin, carbamazepine, lamotrigine and flunarizine. Of the three studies that measured improvement with a validated questionnaire (our primary outcome), one study showed a significant negative (adverse) effect of gabapentin compared to placebo with an increase in TQ score of 18.4 points (SMD 0.82, 95% CI 0.07 to 1.58). A second study did not show a significant effect of gabapentin compared to placebo (difference 2.4 points on the THI SMD-0.11, 95% CI-0.48 to 0.25). When the data of these two studies are pooled no effect of gabapentin is found (SMD 0.07, 95% CI-0.26 to 0.40). A third study comparing gabapentin and placebo did not show a difference using the THI. A meta-analysis of 'any positive effect' (yes versus no) based on a self-assessment score (secondary outcome) showed a small beneficial effect (RD 14%, 95% CI 6% to 22%) for anticonvulsants. However, this effect is not large enough to be considered clinically relevant. It shows that in 14% an improvement can be seen, which in itself is a low number. Secondly, in tinnitus a minor improvement is not always enough to obtain the treatment goal: a decrease in annoyance to a level in which it does not interfere with the patient's quality of life. The treatment goal to be aimed at is near or total eradication of tinnitus annoyance: a meta-analysis of this outcome showed no effect for anticonvulsants (RD 4%, 95% CI-2% to 11%). Side effects of the anticonvulsants used were experienced by 18% of patients.

Overall completeness and applicability of evidence

The results of this review are only applicable to the general tinnitus population. Since tinnitus is a diverse symptom, different subgroups of tinnitus patients may exist, potentially leading to different results in different therapies. Due to the lack of data on factors that could potentially modify the effect of anticonvulsants (such as degree of burden, etiology of hearing loss, duration of tinnitus or whether the patients actively seek help or not), it was not possible to perform subgroup analyses to identify patients that might benefit from anticonvulsants. Piccirillo et al, however, showed a beneficial effect of gabapentin in a subgroup with normal hearing (Piccirillo et al. 2007). It is thus possible that some subgroups might benefit more than others from treatment with anticonvulsants.

Quality of the evidence

Most of the studies included in this review have a moderate or high risk of bias as descriptions of the methodology used are minimal.

Potential biases in the review process

During the review process potential biases were identified both in the individual trials and in the review process itself.

Since tinnitus is a subjective symptom, no gold standard is available to measure the severity of the symptom. Furthermore, there is as yet no consensus regarding the best way to measure treatment effects, making it difficult to interpret and compare results. Validated tinnitus questionnaires are, however, deemed to be more reliable than other subjective measurements such as visual analogue scales and Likert scales. Audiometric measurements of tinnitus are not regarded as reliable outcome parameters. We therefore used validated questionnaires as our primary outcome measure. Of the included studies used the TQ and two the THI as outcome measurement. These are the most used questionnaires, but as mentioned above it remains unclear if these questionnaires are usable in measuring treatment effects (Kamalski et al. 2010).

Due to the large variety of outcome measures used it was not possible to explore publication bias in a funnel plot.

The authors of this review were not blinded to authorship and origin of the included studies since they knew most of the literature before embarking on this review.

Implications for practice

Current evidence regarding the effectiveness of anticonvulsants in patients with tinnitus has significant risk of bias. There is no evidence from studies performed so far to show that anticonvulsants studied (gabapentin, carbamazepine, flunarizine and lamotrigine) have a large positive effect in the treatment of tinnitus but a small effect (of dubious clinical significance) has been demonstrated.

Implications for research

Future trials should be methodologically sound. They should be set up as randomized clinical trials. Patients, treatment providers and outcome assessors should be blinded. Randomization should be performed in a reliable way (e.g. by computer) and the placebo used should be identical to the actual treatment. Results should be analyzed by intention-to-treat.

Consensus should be reached about evaluation methods so that studies can be compared. A first step towards reaching this consensus had been made by the Tinnitus Research Initiative (Langguth et al. 2007). We would recommend following these guidelines

on outcome measurements. The two most often used validated tinnitus questionnaires are the TQ and the THI, so use of at least one of these in evaluations is recommended.

Study populations should be clearly defined in future trials, including degree of burden, etiology of hearing loss, duration of tinnitus and other tinnitus characteristics and whether the patients actively seek help or not.

Future trials should have large enough study populations so that possible effects in subgroups can be evaluated. Smaller trials should only be performed in well-chosen subgroups. Decisions on the type of subgroups should be based (if possible) on earlier studies showing a possible (better) result in these subgroups.

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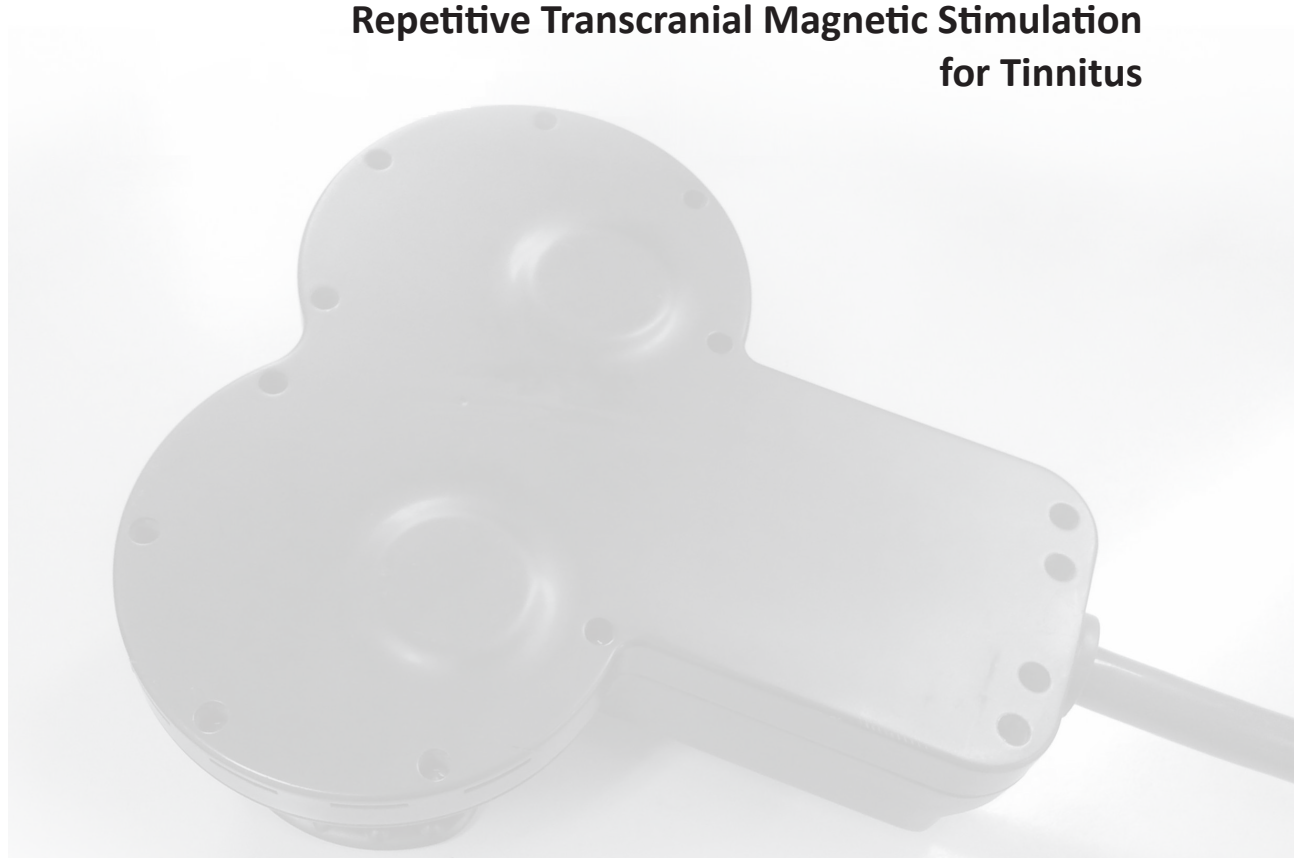
Chapter 6

Repetitive Transcranial Magnetic Stimulation for Tinnitus



C.E.L. Hoekstra, H. Versnel, S.F.W. Neggers, M.E.F. Niesten, G.A. van Zanten, Repetitive transcranial magnetic stimulation of the auditory cortex in tinnitus patients is not effective: a randomized controlled trial, *Audiol Neurotol* 2013;18:362-373

ABSTRACT

Introduction: Although some therapies may be beneficial for some patients in reducing tinnitus, there is no curative therapy. Repetitive transcranial magnetic stimulation (rTMS) has been applied as a treatment for chronic tinnitus, but the effect remains controversial.

Material and methods: Fifty patients were treated with rTMS or placebo. Treatment consisted of 2000 TMS pulses on each auditory cortex, at a rate of 1 Hz and an intensity of 110% of the individual motor threshold, on five consecutive days. rTMS and placebo effects were evaluated directly after treatment, after 1 week, and after 1, 3 and 6 months. Primary outcome was the Tinnitus Questionnaire (TQ). Secondary outcomes were the Tinnitus Handicap Inventory (THI) and a Visual Analogue Scale (VAS).

Results: At none of the follow-up evaluation moments a significant difference between rTMS and placebo was observed with respect to changes in TQ or THI scores relative to pre-treatment scores. Multilevel modeling (MLM) analyses did not show a global treatment effect either. Patients with a higher degree of burden showed a slightly larger improvement after rTMS (only significant on the THI with MLM analyses).

Conclusion: Bilateral low–frequency rTMS of the auditory cortex was not effective in treating tinnitus.

INTRODUCTION

Tinnitus is a phantom auditory perception of meaningless sound in the absence of an external or internal acoustic stimulus. It is a common problem that affects 7-19% of the population (Chung et al. 1984; Coles 1984). Although some therapies may be beneficial for some patients in reducing tinnitus, there is no curative therapy. Psychological therapies (counseling, cognitive behavioral therapy) and tinnitus retraining therapy may diminish tinnitus distress or may improve quality of life by teaching coping strategies, relaxation techniques and distraction skills (Andersson and Lyttkens 1999; Cima et al. 2012; Martinez et al. 2007; Phillips and McFerran 2010). Masking devices, which produce a sound to (partially) mask the tinnitus, might be beneficial to some patients (Hobson et al. 2012), and patients who also have a significant hearing impairment, may benefit from a hearing aid (del Bo and Ambrosetti 2007).

Chronic tinnitus is commonly thought to be a perception, caused by abnormal hyperactivity generated in the auditory cortex and auditory brainstem, as a result of functional reorganization (increased spontaneous firing rate and increased synchronization of spontaneous activity of neurons in the auditory cortex and auditory brainstem), following damage to the cochlea (Eggermont and Roberts 2004; Norena and Eggermont 2003; Ochi and Eggermont 1997; Roberts et al. 2010). This increased synchronous activity hypothesis is supported by results found in magnetoencephalography studies (Schlee et al. 2009; Weisz et al. 2005). The notion that tinnitus corresponds to neural hyperactivity is supported by neuroimaging studies. Even though there are many differences across studies, a general trend can be seen that neural activity across several centers of the central auditory system is enhanced (Lanting et al. 2009). That tinnitus is not solely caused by abnormal hyperactivity in the auditory cortex is shown by abnormal activity in non-auditory areas such as the frontal areas, the limbic system and the cerebellum which was found in neuroimaging studies (Lanting et al. 2009; Leaver et al. 2011).

A possible therapy, aimed at interfering with this maladaptive hyperactivity, is repetitive transcranial magnetic stimulation (rTMS). rTMS at low rates (≤1 Hz) is thought to suppress neural activity (Hallett 2007; Chen et al. 1997). Thus, in case of tinnitus, it might counteract the hyperactivity in the auditory cortex leading to reduction of tinnitus. rTMS as a possible treatment for tinnitus has been studied since 2003 (Plewnia et al. 2003). Cohort studies generally show a small positive effect of rTMS, the largest series (345 patients) shows an improvement of 3 points on the Tinnitus Questionnaire (TQ) (Lehner et al. 2012). Effects are less often measured on the THI or on global assessment measures. Average improvement in two cohort series on the THI was 4 points (23 patients) (Lee et al. 2008; Ting et al. 2011).

One case series includes Visual Analogue Scale (VAS) on annoyance reporting 18 points improvement on a scale of 0-100 in 16 patients (Minami et al. 2011). Six randomized cross-over studies have been performed in small patient groups (Table 1), half of them showing a positive effect (Kleinjung et al. 2005; Plewnia et al. 2007a; Rossi et al. 2007) and half showing no (significant) effect (Piccirillo et al. 2011; Plewnia et al. 2007b; Smith et al. 2007). On average, these studies combined showed a TQ decrease of 4 points (20 patients) (Kleinjung et al. 2005; Plewnia et al. 2007b), an improvement on the THI of 4 points compared to placebo (14 patients) (Piccirillo et al. 2011) and a general VAS improvement of 11 points compared to placebo (20 patients) (Rossi et al. 2007; Smith et al. 2007).

Table 1 Randomized controlled cross-over trials on the effect of low-frequency rTMS on tinnitus

Study	n	Focus of treatment	Outcome parameter	Results rTMS	Results placebo	Conclusion authors
Kleinjung 2005	14	Most active PAC on PET	TQ	-3	No numbers placebo	Significant reduction
Piccirillo 2011	14	Left TP region	THI	-8 (51 → 43)	-4 (51 → 47)	No more effective than placebo
Plewnia 2007a*	9	Most active TP cortex on PET	VAS-LC (-150/+150)	-28**	-10**	Greater reduction compared to sham
Plewnia 2007b*	6	Most active TP cortex on PET	TQ	-7** (35** → 28**)	-1** (35** → 34**)	Moderate reduction of tinnitus, only in two subjects clinically relevant
Rossi 2007	16	Left TP	VAS (0-100)	-20 (67 → 47)	-7 (67 → 60)	Significant effect
Smith 2007	4	Most active PAC on PET	TSIQ VAS (0-100)	-3 (29 → 26) -3 (54 → 51)	-1 (29 → 28) +1 (54 – 55)	Modest, non significant, response to treatment

Values represent differences in scores, with 'baseline score → score after treatment' in parentheses. PAC = Primary auditory cortex; PET = positron emission tomography; TP = temporoparietal; VAS-LC = VAS for loudness change; TSIQ = Tinnitus Severity Index Questionnaire.
* = all subjects of the 2nd study had already participated in the 1st study
** = no exact numbers given in article, number estimated from graph

Results of cross-over studies must be considered with care because patient blinding might not be adequate (the difference between real and placebo rTMS could be obvious for a subject undergoing both forms) and carry-over effects may exist. Parallel blinded randomized controlled trials (RCTs) are preferred. Thus far, four parallel RCTs on low-frequency rTMS have been performed (Anders et al. 2010; Khedr et al. 2008; Langguth et al. 2012; Marcondes et al. 2010). Two of these studies report a significant effect of rTMS compared to placebo (Khedr et al. 2008; Marcondes et al. 2010). One study shows an improvement for both rTMS

and placebo, but does not compare the groups to each other (Anders et al. 2010). The last study shows no significant difference between rTMS and placebo treatment (Langguth et al. 2012). A Cochrane review evaluated the first three of these studies on mean differences (with 95% confidence intervals) between rTMS and placebo scores after treatment which gives less positive results. They conclude a partial effect of rTMS in one study and no effect in the other two studies and they advise more prospective RCTs with large sample sizes, using validated tinnitus-specific questionnaires (Meng et al. 2011).

Optimal rTMS treatment conditions remain uncertain and conditions have been used variably across studies. In this trial patients are treated with 1Hz rTMS because this is thought to lead to suppression of neural activity (Hallett et al. 2007) and thus suppression of hyperactivity underlying tinnitus. Other parameters for rTMS set up were chosen in line with most previous studies to aid comparability: patients were treated on 110% of the motor threshold with a figure-of-eight coil (Kleinjung et al. 2005; Kleinjung et al. 2007; Langguth et al. 2007; Smith et al. 2007). The handle of the coil pointed upward (Kleinjung et al. 2005; Kleinjung et al. 2007; Langguth et al. 2007). The duration in this study (1 week) is comparable to durations used in previous studies (1-2 weeks) as well.

The optimal hemisphere for rTMS is not obvious. Previous studies have stimulated the most activated brain region seen on functional imaging scans (Kleinjung et al. 2005; Langguth et al. 2007; Plewnia et al. 2007a; Plewnia et al. 2007b; Smith et al. 2007), the left cortex because in functional imaging studies most activation was found on this side (De Ridder et al. 2005; Khedr et al. 2008; Kleinjung et al. 2007; Lehner et al. 2012; Marcondes et al. 2010; Rossi et al. 2007), or the contralateral auditory cortex (De Ridder et al. 2005). Our study is the first using bilateral rTMS on tinnitus patients. This way we stimulate with certainty the optimal hemisphere (if there would be one). Both cortices receive input from a single cochlea (Langers et al. 2007). Thus theoretically, a lesioned cochlea might lead to tinnitus-related hyperactivity ipsilateral, contralateral or bilateral in the auditory cortex. In the latter case, bilateral rTMS would be preferred above unilateral rTMS. Furthermore we have used the three most commonly used evaluation methods (TQ, THI and Visual analogue scale (VAS)), to measure effects, making it possible to compare our study with most of the previous studies.

Our study addresses the hypothesis that low-frequency rTMS is effective in reducing chronic tinnitus. Also, by stimulating bilaterally we think that we will be able to show the best possible effect compared to other studies.

MATERIAL & METHODS

Study design, participants and randomization

This study was performed at the University Medical Center Utrecht (UMC Utrecht) between June 2007 and June 2011, as a randomized double blind placebo controlled clinical trial in chronic tinnitus patients. The study was performed in accordance with the Declaration of Helsinki, ethical approval was obtained from the medical ethical committee of the UMC Utrecht (07-286/O). Patients were included when written informed consent was received. The trial was registered at the Dutch trial register (ID NTR1293) and on clinicaltrials.gov (ID NCT00668720).

Patients who were analyzed at the Tinnitus Care Group of the Otorhinolaryngology department of the UMC Utrecht were considered for inclusion. Patients are considered eligible for assessment at this Tinnitus Care Group when they have a non-fluctuating tinnitus of at least two months duration. The shortest tinnitus duration at inclusion for this study turned out to be eight months. Patients with a treatable cause of their tinnitus (e.g., cerumen) or psychiatric disease were excluded. Other exclusion criteria were based on TMS safety guidelines: use of anticonvulsant or psychotherapeutic medication that lower seizure thresholds, history of or family members with epilepsy, migraine, structural brain changes, severe internal or heart disease, alcohol or drug abuse, irremovable metal objects in the body, metal workers and pregnancy (Wasserman 1998).

Patients were randomized in a 1:1 ratio by an independent epidemiologist to placebo or real rTMS treatment. Randomizations were performed through a block design per group of eight patients with four patients being allocated by computer to rTMS and four to placebo. Patients and outcome assessors were blinded to treatment group allocation. The investigator performing the treatment was not blinded because the difference between rTMS and placebo treatment is recognizable by the investigator. Patients and investigators were instructed not to talk about the treatment or effect to protect patient blinding.

Neuronavigation and positioning

To achieve optimal coil positioning to the location of the patient's primary auditory cortex, image-guided stereotaxy was performed with the aid of a frameless stereotactic device that uses structural imaging data to guide TMS coil placement (the Neural Navigator, Brain Science Tools BV, the Netherlands (http://www.neuralnavigator.com)) (Neggers et al. 2004). The location of the individual patients' primary auditory cortex was determined on a structural T1 weighted magnetic resonance images (MRI) scan with gadolinium contrast which was made during the diagnostic stage (Philips 1.5 Tesla MRI scanner, voxel size 1.25 x 1.25 x 1.25 mm, no slice gap). On this scan Heschl's gyrus was located conform MRI-determined landmarks for this gyrus (Abdul-Kareem and Sluming 2008). The primary auditory cortex lies within this gyrus with a variable position (Abdul-Kareem and Sluming 2008). Because the figure-of-eight coil stimulates an area of approximately 3 x 2 cm at the cortex (Londero et al. 2006), the primary auditory cortex is assumed to be included in the field by directing rTMS to the centre of Heschl's gyrus. The anatomical scan was transformed to a 3D-rendered image of skin surface on which the area of interest and craniotopic landmarks (tip of the nose, medial and lateral canthus of the eye and onset of the pinna) were marked. On the first treatment day the craniotopic landmarks were measured directly on the patient's head with a 3D digitizer pen (DriveBAY position tracker system, Acension Technologies, Merrillville, Indiana), subsequently, the location on the scalp overlying the auditory cortex was found by stereotactic navigation. This spot was marked with ink, shaved and a neurosurgical marker was placed in order to identify the spot the following days.

Patients were seated in a desk chair with their chin in a jaw support and with their forehead secured with a band against a support bar. Using a template, the coil was positioned above the marked location with the handle pointing upward perpendicular to the skull. It was held in place against the patient's head with a mechanical arm. Patients were provided with ear plugs to minimize the noise dose and possible residual inhibition (i.e. the reduction of tinnitus sensation after exposure to sound).

rTMS protocol

Patients were treated with low-frequency 1 Hz rTMS or placebo for 2000 pulses on each auditory cortex. A break of 5-10 minutes was used to switch the coil from one hemisphere to the other and to allow the patient to relax. Treatment was performed on 5 successive days around the same time. All patients were treated by investigator CH or HV.

rTMS was performed with a Magstim Rapid^2 magnetic stimulator with an air-cooled 70-mm figure-of-eight coil (Magstim Company Limited, UK) at an intensity of 110% of the patient's motor threshold (MT). MTs were determined in every rTMS patient on the first treatment day in a descending staircase method until the lowest intensity was reached at which 5 of 10 consecutive pulses induced a visible twitch in the contralateral hand (Schutter and van Honk 2006). On each hemisphere the intensity was set according to the MT obtained on that hemisphere.

Placebo treatment was performed with a placebo coil (Magstim Company Limited, UK) replicating the appearance, sound emission, stimulation of superficial tissue (muscles) and operation of the TMS coil without stimulating cortical tissue. Motor thresholds were not determined in placebo patients to prevent them from perceiving the difference between real and placebo TMS, and thus protecting placebo blinding. Placebo stimulation intensities were determined according to the stimulation intensities used on already included real rTMS

patients so that they were comparable in average intensity as well as in range. The stimulation intensity was one-to-one matched to already included rTMS patients in 14 placebo patients and randomly decided in 11 placebo patients because less rTMS patients had been treated at that moment. Neuronavigation procedure and treatment schedule were similar in the two treatment groups.

Data acquisition

Tinnitus burden was measured through the TQ, THI, and a VAS. The TQ is a 52-item self-response questionnaire with three answer possibilities (true, partly true, false) and a total score from 0 to 84 (Hallam et al. 1988). The THI is a 25-item self-response questionnaire with three answer possibilities (yes, sometimes, no) and a score range of 0-100 (Newman et al. 1996). The VAS is a visual "burden thermometer", analogous to a distress thermometer used in cancer patients, asking the patients to indicate the amount of overall burden experienced that day on an 11-point scale, ranging from 0-10 (no to extreme distress), with half scores when patients scored in between numbers (Roth et al. 1998; Tuinman et al. 2008). Possible co-morbid anxiety and depression were measured with the State Trait Anxiety Index (STAI) (disposition and state subscale), and with the Beck Depression Index (BDI). Pure-tone-audiometry and tinnitus analysis (pitch and loudness matching) were all performed by one of two audiology assistants trained in tinnitus analysis, who were blinded for treatment type. Potential octave ambiguity was tested as part of tinnitus pitch matching. Tinnitus loudness was matched at the pitch-matched frequency. When a pitch-match could not be obtained, the loudness was matched with a 1000 Hz pure tone. Testing was done in a soundproof cabin with TDH 39 earphones on a Decos Audiology audiometer (Decos Technology Group, Noordwijk, the Netherlands) which is compliant with ISO 389 standards. Pure-tone-audiometry was performed according to international standards (ISO 8253-1).

Outcomes

rTMS and placebo effects were evaluated directly after treatment, after 1 week, and after 1, 3 and 6 months. Patients returned for audiometric testing after 1 week, 3 and 6 months. They received a booklet on the final treatment day containing questionnaires for the coming period, with an instruction when to complete these. They returned these at the next visit. Primary outcome was the TQ. Secondary outcomes were the THI and VAS.

Statistics

We considered a 25% improvement to be clinically relevant. Power calculation (power 80%, alpha 0.05) showed that 26 patients per group were needed to detect a 25% improvement on the TQ. This analysis was based on the mean TQ score of patients that had been seen

at the Tinnitus Care Group of the UMC Utrecht when the study was planned (mean TQ score 50, standard deviation 14). Baseline data were analyzed with independent two-tailed t-tests and chi^2 tests. Change in scores and comparison between scores were analyzed using independent two-tailed t-tests. Comparisons between groups that reached a clinical significant improvement of 25% were performed with chi^2 tests. These analyses were conducted with SPSS 20.0 (SPSS Inc., Chicago, Il, USA). The time course of the effects over half a year and the possible influence of patient factors on the effect of rTMS were analyzed with multilevel modeling (MLM). Compared to ANOVA and linear regression, MLM has several advantages: no sphericity requirements for data-distributions, more powerful in detecting effects and capable of analyzing incomplete data (Quené and Van den Bergh 2004). p-values were computed on the basis of 10,000 Markov chain Monte Carlo samples. MLM analyses were conducted in the R programming environment for statistical analysis (http://www.r-project.org). The dependent factor in the MLM analysis was a change of TQ (or THI) relative to baseline; independent factors were treatment, time and a third factor such as TQ (or THI) at baseline, age or tinnitus duration. Interaction between the three factors was included in the analysis. All effect analyses were performed by an investigator (HV) who was blind to treatment allocation. For the analyses he received only the scores of the outcome parameters with a treatment code (A/B) and no data that could disclose treatment type of individual patients (e.g., gender).

RESULTS

Patients

Two-hundred-fourteen tinnitus patients were seen between June 2007 and October 2010 at the tinnitus clinic of the UMC Utrecht. The patient inclusion ended in October 2010 because the enrolment of 52 patients was reached. Two patients withdrew after they had given consent, but because they had already been randomized they were not replaced. Figure 1 shows the trial's patient selection, including reasons for not participating. Forty-one males and nine females were included: 26 patients received rTMS and 24 patients received placebo treatment. Table 2 shows the baseline values of the 50 participants. Groups were comparable at baseline for all parameters but tinnitus location (more patients with unilateral tinnitus

Table 2 Demographic, clinical and treatment characteristics of included patients

Characteristics	Total n = 50	rTMS n = 26	Placebo n = 24	p value
Sex †				0.001
Male	41 (82%)	26 (100%)	15 (63%)	
Female	9 (18%)	0 (0%)	9 (27%)	
Age in years	52 (12)	50 (12)	55 (12)	0.15
Subjective hyperacusis †	16 (32%)	8 (31%)	8 (33%)	0.85
Duration of tinnitus in months ‡	46 (8-420)	58 (8-240)	38 (12-420)	0.78
Number of sounds ‡	1 (1-4)	1 (1-4)	1 (1-3)	0.23
Tinnitus location †				0.011
unilateral	20 (40%) [7:13]	6 (23%) [3:3]	14 (48%) [4:10]	
bilateral / in the head	30 (60%)	20 (77%)	10 (42%)	
Averaged (0.5, 1, 2, 4kHz) pure-tone-hearing loss (dB HL)				
Right	27 (23)	24 (17)	31 (28)	0.28
Left	31 (27)	27 (25)	36 (30)	0.25
Tinnitus pitch (Hz)	6640 (4195)	7115 (4620)	6119 (3716)	0.44
Tinnitus loudness (dB HL)	61 (25)	54 (28)	69 (18)	0.05
TQ	40 (16)	38 (14)	43 (14)	0.25
THI	45 (21)	45 (17)	44 (18)	0.84
VAS burden	6.1 (2.0)	6 (2)	6 (2)	0.41
BDI	11 (8)	11 (7)	11 (9)	0.71
STAI disposition	38 (11)	37 (10)	40 (12)	0.36
STAI state	37 (10)	35 (8)	39 (11)	0.12
Stimulation intensity	66 (13)	66 (13)	65 (13)	0.95

Values represent means with SD in parentheses, unless stated otherwise . dB HL = dB hearing level; Hz = Hertz
† numbers with percentage in parentheses. Values in square brackets denote right:left ratio.
‡ medians with ranges in parentheses

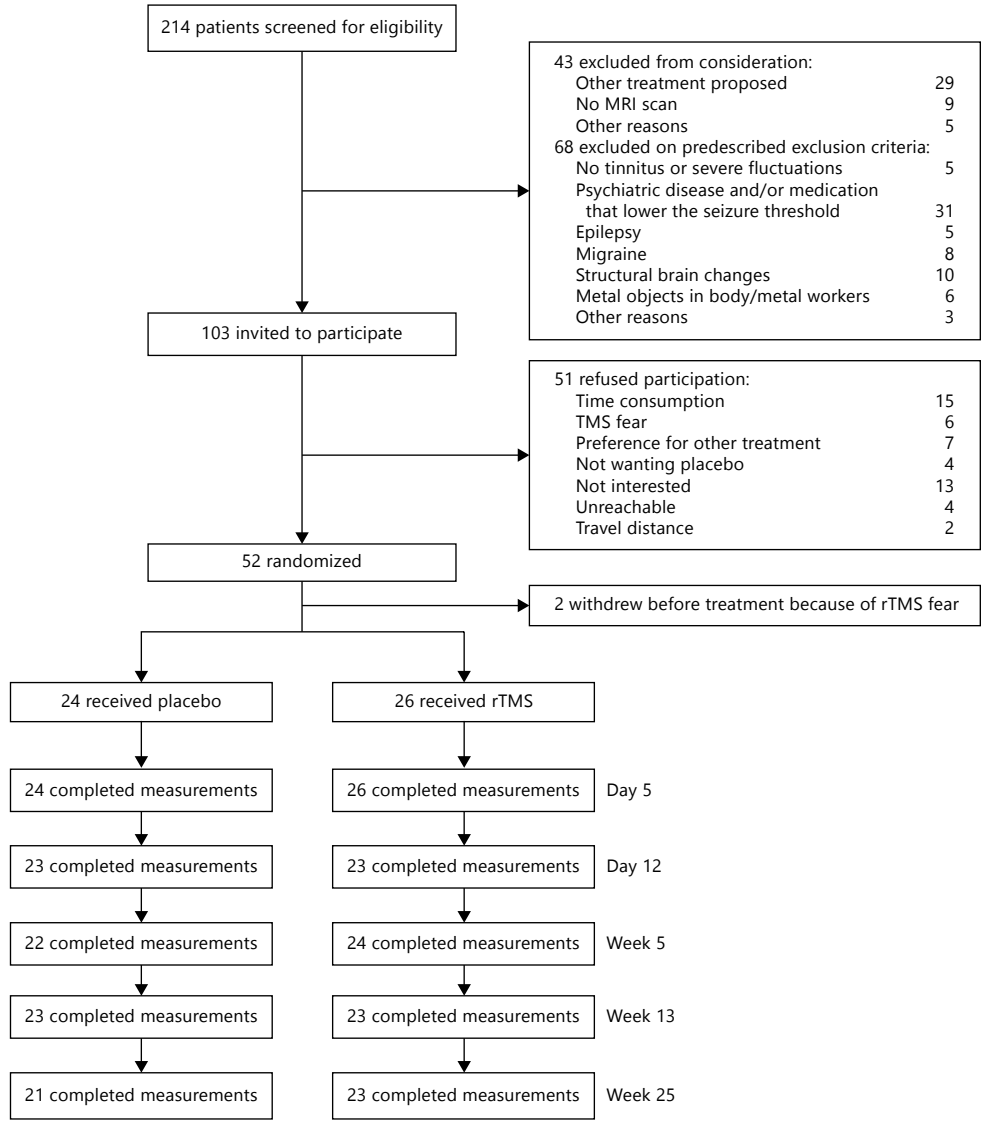


Figure 1 Flow chart of patient selection and compliance with follow-up. The measurements refer to the TQ. Followup times are indicated with respect to the first day of treatment (day 1).

in placebo group) and gender (all females were in placebo group). As the allocation was randomized, it was by chance that all female subjects received placebo treatment. TQ scores ranged from 11 to 72, with a high and a low cluster of scores around a less frequent score of 35 to 42 (figure 2).

Compliance with follow-up was high: 6.7% of primary outcome data (TQ) are missing, with 0% on day 5 and a maximum of 15% in week 25. One patient dropped out, he stopped

on the second day of rTMS treatment because of side effects and did not comply with follow-up. There is no difference between missing data rates in the rTMS and the placebo group (figure 1). Patients who had missing data were at all time points comparable to included patients on baseline TQ, THI and VAS scores, age, gender, tinnitus pitch and duration. Patients with missing data on day 12, week 5 and week 13 had significantly lower tinnitus loudness (8, 37 and 45 dB below the average loudness of complying patients).

Patients were adequately blinded for treatment type, shown by their inability to identify their treatment type. Twenty-seven patients (56%) correctly identified their treatment type, which did not significantly differ from chance (binomial statistics, p>0.2).

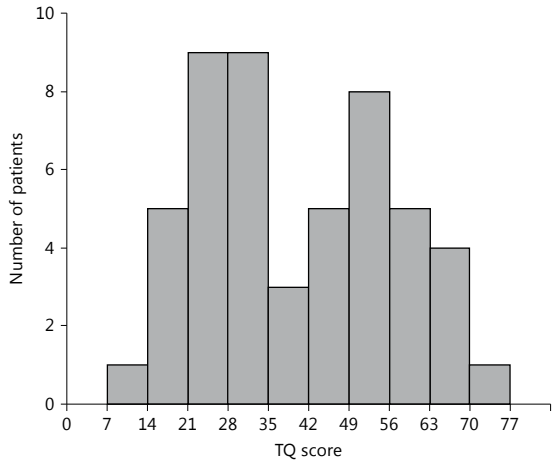


Figure 2 Distribution of TQ scores at baseline obtained from all patients participating in the trial (n = 50). The scores were obtained shortly before treatment started (typically the day before the first day of treatment).

Primary endpoint: effect of rTMS on TQ

TQ, THI and VAS scores are shown in figure 3 and table 3. Average TQ scores showed a small improvement directly after 5 days of both rTMS (2 points) and placebo (1 point) treatment. This 1-point difference was not significant (*t*-test, p=0.80), neither was the difference between the absolute scores of the groups (*t*-test, p=0.21). When looking at the pre-defined clinically relevant effect of at least 25% improvement (10 points), more patients in the placebo than in the rTMS group (four versus three patients) reached this effect. After this initial effect, scores increased slightly in both groups, after which they decreased (improved) again in the real rTMS group and continued to increase in the placebo group. At no time point the difference between rTMS and placebo scores was significant with respect to a change from baseline.

When comparing absolute scores there was no significant difference either at any time point, except at 6 months [173 days] (p=0.004; note this is not statistically significant when correcting for multiple comparisons with α=0.0016). Multilevel modeling analysis corroborated these results (table 4). No global effect of treatment was found (p=0.87). Confirming the rising scores for mainly the placebo group during the long-term follow-up, a significant global effect of time was found for the change from baseline (p=0.008). Scores in the rTMS group slightly varied up and down, whereas scores in the placebo group increased continuously leading to a significant interaction effect of treatment and time (p=0.04). Note that the slopes of time

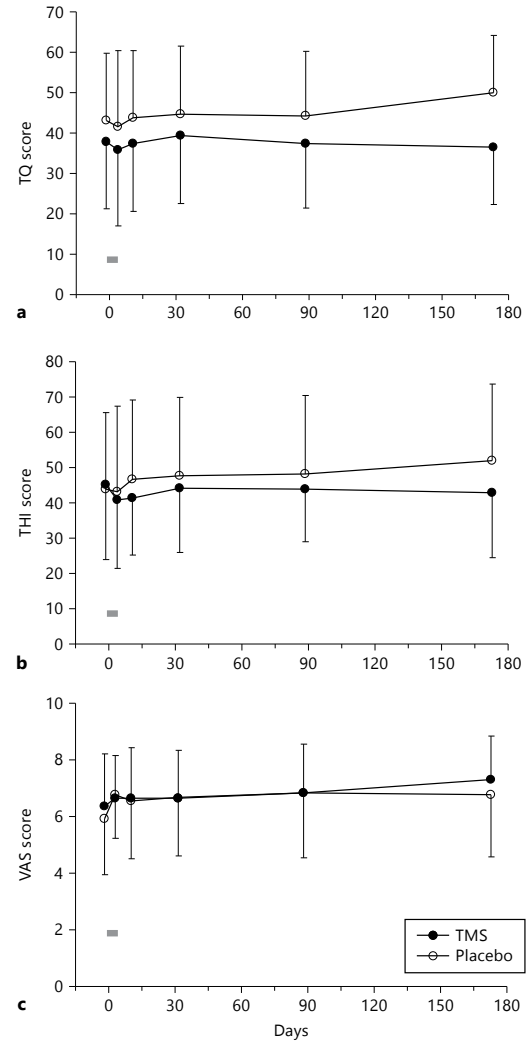


Figure 3 TQ (a), THI (b) and VAS (c) scores averaged across patients per treatment condition (TMS or placebo) immediately before and at various time points after treatment. The number of patients per data point slightly varied, as indicated in the compliance chart of figure 1. Error bar: SD. Grey bar: 5-day period of treatment.

(0.028) and interaction time*treatment (-0.029) virtually cancel each other which reflects the lack of an average change of TQ within the rTMS treatment group.

Table 3 Primary and secondary outcomes for tinnitus severity on all time points

	baseline	directly after (day 5)	after 1 week (day 12)	after 1 month (day 33)	after 3 months (day 89)	after 6 months (day 173)
Tinnitus questionnaire						
TQ real	38 (16)	36 (14)	37 (14)	40 (16)	37 (14)	37 (15)
TQ placebo	43 (17)	42 (19)	44 (17)	44 (17)	44 (16)	50 (14)
p value 1	0.25	0.21	0.17	0.27	0.12	0.004
p value 2		0.80	0.93	0.78	0.82	0.32
Tinnitus Handicap Inventory						
THI real	45 (21)	41 (19)	41 (16)	44 (18)	44 (15)	43 (18)
THI placebo	44 (22)	43 (24)	47 (23)	48 (22)	48 (22)	52 (22)
p value 1	0.84	0.70	0.37	0.56	0.45	0.14
p value 2		0.09	0.08	0.22	0.42	0.06
Visual Analogue scale						
VAS real	6.4 (1.6)	6.6 (1.4)	6.6 (1.4)	6.7 (1.6)	6.8 (1.4)	7.3 (1.5)
VAS placebo	5.9 (2.0)	6.8 (1.5)	6.6 (2.1)	6.7 (2.1)	6.8 (2.3)	6.8 (2.2)
p value	0.43	0.77	0.90	0.97	0.98	0.35
p value 2		0.38	0.42	0.37	0.32	0.77

Values represent mean scores with SD in parentheses and are based on all available patients. p value 1 = Difference between absolute scores; p value 2 = difference between change in scores.

Secondary endpoints: effect of rTMS on THI and VAS

THI scores showed, similar to TQ scores, a slightly larger, not significant improvement after both real (4 points) and placebo (1 point) treatment (p=0.09 on difference between changes in scores, and p=0.70 on difference between absolute scores). Six patients in the rTMS group reached the pre-defined clinically relevant effect of at least 25% improvement (11 points). The difference with the placebo group (three patients who reached this effect) was not significant (p=0.47). The time course of the scores on the THI showed a similar (not significant) pattern, with an increase of scores after the initial effect, a subsequent improvement in the long term in the real rTMS group and continuous increase of scores in the placebo group. For the difference between change of scores a possible trend for an effect of TMS can be observed (p=0.09 at day 5, p=0.08 at day 12, p=0.06 at day 173). Also similar to TQ scores, no global effect of treatment was found with MLM analyses (p=0.13), a significant global effect of time was observed (p= 0.006), as was a significant treatment*time (p=0.05) (see table 4).

VAS scores, reflecting the patient's own assessment of tinnitus distress, did not show a benefit at all. Scores increased slightly in both groups directly after treatment (rTMS 0.3 points, placebo 0.7 points) and gradually increased over 6 months for both rTMS and placebo, with no significant group differences at any time point.

Table 4 Multilevel modeling analyses

Factor	Slope	p
Multilevel analysis TQ change		
Intercept	-0.30	0.82
Treatment	**0.23**	**0.87**
Time	*0.028*	*0.008*
TQ_0	-0.044	0.51
Treatment*time	*-0.029*	*0.04*
Treatment*TQ_0	-0.16	0.10
Time*TQ_0	*-0.0012*	*0.05*
Treatment*time*TQ_0	0.0013	0.13
Multilevel analysis THI change		
Intercept	1.03	0.45
Treatment	**-2.9**	**0.13**
Time	*0.032*	*0.006*
THI_0	-0.0095	0.90
Treatment*time	-0.021	0.22
Treatment*THI_0	*-0.17*	*0.05*
Time*THI_0	*-0.0012*	*0.03*
Treatment*time*THI_0	0.0006	0.47

Time: 5, 12, 33, 89 and 173 days. Treatment: 0 = placebo, 1 = TMS. TQ0 = Baseline TQ corrected for median; THI0 = baseline THI corrected for median.

Effects in subgroups

For patients with severe tinnitus (baseline TQ scores above 35, n=26) the difference in improvement in scores between rTMS and placebo was larger than for the entire group: the TQ improved 5 points after rTMS, compared to 1 point for placebo, which was however not significant (*t*-test, p=0.12). The THI improved 5 points for rTMS and was unchanged for placebo (*t*-test, p=0.15). Multilevel modeling analyses of TQ and THI showed a trend for a greater effect of treatment for greater baseline tinnitus severity, this interaction was significant for the THI (p=0.05), but not for the TQ (p=0.10).

Multilevel modeling analyses on the TQ score did not show an influence of the factors "age", "tinnitus duration", "tinnitus laterality", "tinnitus pitch", "tinnitus loudness", "hearing loss", "subjective hyperacusis", "BDI-score" or "STAI-score" on the effect of rTMS (p>0.1). Because all female patients received placebo treatment, a subgroup analysis for gender was not possible. When comparing the outcomes of only the male patients between both groups, the same result as shown in Table 4 was obtained: no significant effect of treatment (p=0.9).

Side effects

In general, treatment was tolerated well. Five patients experienced side effects of rTMS (all headache, 1 additionally dizziness and 1 additionally experienced a sensation of “licking on a battery”). One patient experienced side effects of placebo (headache).

DISCUSSION

This study does not show an effect of bilateral low-frequency rTMS of the auditory cortex. There was no effect of rTMS for the entire group of tinnitus patients on any outcome parameter (TQ, THI or VAS), though a trend for a positive effect could be observed on the THI. In patients with severe tinnitus rTMS tends to have a positive effect, which is only significant on one secondary outcome parameter (THI) and very small (5 points TQ-11% improvement and 5 points THI- 13% improvement) and therefore not clinically relevant. An effect of treatment versus time was found in the MLM analyses but this is caused by a deterioration of scores in the placebo group and not by an actual positive effect in the treatment group.

The slight improvement we found on the TQ (2 points) and THI (4 points) is comparable to improvements found in cohort and cross-over studies (TQ 3-4 points, THI 4-8 points). Including our study, five parallel RCTs on low-frequency rTMS have been performed (table 5). All studies show an improvement in the rTMS group, and all studies but one (Marcondes et al. 2010) show an improvement in the placebo group. This positive effect of rTMS is, in agreement with our study, only small in two of these studies (Anders et al. 2010; Langguth et al. 2012). One of these studies shows, in line with our study, no significant difference between rTMS and placebo treatment (Langguth et al. 2012), the other shows that

Table 5 Randomized controlled parallel trials on the effect of low-frequency rTMS on tinnitus

Study	N	Focus of treatment	Outcome parameter	Results rTMS	Results placebo
Anders 2010	52*	Left PAC	THI TQ VAS (0-100)	-5 (37 → 32) -4 (32 → 28) -4 (56 → 52)	-4 (27 → 23) -2 (23 → 21) -2 (36 → 34)
Khedr 2008	32	Left temporoparietal cortex	THI	-19 (58** → 39**)	-6 (45** → 39**)
Langguth 2012	92	Left temporal cortex	TQ	-2 (39 →37)	-1 (38 → 37)
Marcondes 2010	19	Left temporoparietal junction	THI VAS-L	-11 (30 → 19) -2 (7.5** → 5.5**)	0 (29 → 29) 0 (7** → 7**)
This study	50	Bilateral PAC	THI TQ VAS (0-10)	-4 (45 → 41) -2 (38 → 36) +0.2 (6.4 → 6.6)	-1 (44 → 43) -1 (43 → 42) +0.9 (5.9 → 6.8)

Values represent difference in score , with ‘baseline score → score after treatment’ in parentheses.
PAC = primary auditory cortex, THI = Tinnitus Handicap Inventory, TQ = Tinnitus Questionnaire
VAS(-L) = visual analogue scale (for loudness)
* 10 patients withdrew, and are not included in analyses (4 patients withdrew in rTMS group, including 2 because of tinnitus worsening, and 6 patients withdrew in placebo group)
** no exact numbers given in article, number estimated from graph

the improvement for both rTMS and placebo is significant compared to baseline, but does not compare the groups to each other (Anders et al. 2010). As the improvements in this study are quite similar (5 versus 4 points on the THI and 4 versus 2 points on the TQ) it seems most probable that the difference between groups is not significant as well. The two other studies do show a significant effect of rTMS compared to placebo, and the improvement after rTMS is notably higher (11-19 points THI) than in above studies not finding an effect (4-5 points THI) (Khedr et al. 2008; Marcondes et al. 2010).

Different explanations might be possible for the opposing outcomes in the five parallel RCTs. The most obvious difference between the trials is the location of stimulation. The two trials finding an effect stimulated the temporoparietal junction, while the three trials not finding an effect stimulated the primary auditory cortex. The auditory cortex is thought to play an important role in tinnitus, but there is growing evidence that an interplay of auditory cortex with limbic system, prefrontal cortex and parietal cortex determines tinnitus distress (De Ridder et al. 2011; Leaver et al. 2011; Roberts et al. 2010; Schlee et al. 2009). The parietal cortex and its connections to the auditory cortex could be involved in tinnitus through the mediating effect that the parietal cortex has on auditory attention (Cuny et al. 2004; Searchfield et al. 2007). rTMS to these areas could therefore mitigate patient's reaction to tinnitus, leading to a reduction of the perception of tinnitus. Considering the found effect in two parallel RCTs stimulating their patients at the temporoparietal junction (Khedr et al. 2008; Marcondes et al. 2010) this might be a more effective target for rTMS than the auditory cortex specifically.

Another possible explanation for the opposing outcomes might be found in differences in study populations. Different factors have been described to have an influence on the effect of rTMS. The severity of tinnitus has been reported to be a strong positive predictor for rTMS outcome (Lehner et al. 2012). We confirmed this relationship with the relatively sensitive multilevel modeling approach, but without a clinically relevant effect. Tinnitus severity does not seem to play a role, though, in the different outcomes among the five RCTs: compared to the other studies one of the studies showing effect had the lowest THI scores (Marcondes et al. 2010) and one of the studies not finding effect (this study) had the second to highest THI score (table 5). In this study we did not find an influence of the factors age, tinnitus duration, tinnitus laterality, tinnitus pitch, tinnitus loudness, hearing loss, subjective hyperacusis, BDI-score or STAI-score on the effect of rTMS. Of these factors three factors (tinnitus duration, hearing loss, and depression) may be considered in explaining the different outcomes between the five studies. The study of Khedr et al. showed a positive effect of rTMS and treated a population with a fairly short tinnitus duration (greatest proportion of patients had a duration (much) shorter than 4,5 years). A shorter duration of tinnitus has been observed to have a positive effect on treatment outcome (De Ridder et al. 2005; Khedr et al. 2008; Kleinjung et al. 2007; Plewnia et al. 2007b), although other studies do not find this effect

(Lehner et al. 2012; Smith et al. 2007), including one study (Lehner et al. 2012) correcting for possible confounding effects. The study of Marcondes et al. showed a positive effect of rTMS and was performed in only normal hearing subjects. Hearing loss has been described in two studies (Kleinjung et al. 2007; Smith et al. 2007) to potentially have a negative influence on rTMS effects (one with potential bias because of analyses of only treatment responders (Kleinjung et al. 2007)). In contrast one study correcting for possible confounding effects (Lehner et al. 2012) did not find a relationship. Along that line and opposing a positive effect of normal hearing, the study of Langguth et al. included only patients with near to normal hearing (average thresholds 16 dB HL in placebo patients and 14 dB HL in rTMS patients), but did not find an effect of rTMS. It could be postulated that rTMS for tinnitus exerts its effect by a positive effect on depression. The studies not finding an effect indeed seemed to include patients without much depression (in our study patients had low BDI scores, the study of Langguth et al. excluded patients with clinically relevant psychiatric morbidity). It cannot be demonstrated however that studies finding an effect included depressed patients. The study of Marcondes et al. excluded patients with a psychiatric disease based on a psychiatrist's evaluation, the study of Khedr et al. does not include information on potential depression and the cross-over studies finding an effect either excluded depressed patients (Rossi et al. 2007c) or did not include information on depression (Kleinjung et al. 2005; Plewnia et al. 2007a). As for age, tinnitus pitch, tinnitus loudness, hyperacusis, and anxiety, these five parallel RCTs do not give sufficient information to compare them for a possible effect of these factors on the effect of rTMS treatment.

Our study differs from the other four RCTs because we stimulated our patients bilaterally. Because we did not find an effect of rTMS we have to reject our hypothesis that bilateral stimulation would be preferred. All in all, study population factors do not seem to play a dominant role in the differences between the effects found in the RCTs.

Most studies on the effect of TMS on tinnitus have focused on low-frequency rTMS, but it might be possible that a different mode of TMS has a better effect. In addition to above RCTs on low-frequency rTMS, two RCTs on theta burst rTMS have been performed and two RCTs on high-frequency rTMS. One study finds a significant improvement for theta burst rTMS compared to placebo (Chung et al. 2012), the other did not find a difference between theta burst rTMS and placebo (Plewnia et al. 2012). The two RCTs on high-frequency rTMS both found a significant effect Fregni et al. 2006; Khedr et al. 2008). A second parameter that might influence rTMS effectiveness but that has not been varied often is the duration of rTMS. The RCT's performed until now have treated for one (Marcondes et al. 2010; our study) or two weeks (Anders et al. 2010; Khedr et al. 2008; Langguth et al. 2012). For depression it has been stated that results may be better after longer duration of treatment (>2 weeks) (Loo and Mitchell 2005). Potentially this would apply to tinnitus as well.

This study was powered to find an effect that we believed to be clinically relevant (25% improvement, calculation based on the TQ). This study was not powered to find very small effects, such as the effects shown in this study (2 and 4 points improvements directly after TMS on the TQ and the THI), which are clinically irrelevant even if they had been statistically significant in a much larger population.

Concluding, in this study low-frequency rTMS was shown not to be effective in treating tinnitus. Two other RCTs performed so far, confirm this ineffectiveness. Although positive trends may be observed in studies in favor of rTMS compared to placebo, the found effects are so small that they should be considered clinically irrelevant. Considering the found effect in two parallel RCTs stimulating their patients at the temporoparietal junction, this might be a more effective target for rTMS than the auditory cortex specifically. Though it seems that low-frequency rTMS has been adequately shown not to be effective in the general population of tinnitus patients, it remains debatable if rTMS might be effective in certain subgroups of patients or with a different pulse frequency or location protocol. It is recommended therefore that future studies will only be performed in well defined subgroups or with different treatment protocols. An interesting example of a subgroup which (as our study hinted at) might benefit from rTMS, are patients with a higher degree of tinnitus burden.

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Chapter 7

Measuring Treatment Effects in Tinnitus Therapies

Kamalski DM, Hoekstra CE, van Zanten BG, Grolman W, Rovers MM., Measuring disease-specific health-related quality of life to evaluate treatment outcomes in tinnitus patients: a systematic review., *Otolaryngol Head Neck Surg*. 2010 Aug;143(2):181-5.

ABSTRACT

Objective: To identify all disease specific HR-QoL instruments used to assess tinnitus in clinical trials and detail their psychometric properties.

Data Sources: A literature search was performed in the bibliographical databases of PubMed and Embase to identify all articles using specific HR-QoL instruments in tinnitus trials. Review Methods: The HR-QoL instruments used in these articles were investigated in more detail, focusing on characteristics and psychometric values by two independent reviewers.

Results: Seventeen studies were identified by the systematic search. The most used HR-QoL questionnaire was the Tinnitus Questionnaire (TQ), followed by the Tinnitus Handicap Inventory (THI), Tinnitus Reaction Questionnaire (TRQ), and the Tinnitus Handicap Questionnaire (THQ). Internal consistency (Cronbach alpha > 0.9) and reproducibility (>0.8) were high for all questionnaires, and there was heterogeneity in responses between patients, endorsing the use of these questionnaires for discriminative purposes. However, the responsiveness, i.e., the usefulness of these questionnaires in evaluating treatment effects, is not known yet.

Conclusion: The HR-QoL instruments used in tinnitus trials appear not to be validated to measure effectiveness of interventions. Using tests or instruments that are valid and reliable is a crucial component of research quality, and both should therefore be studied before final conclusions can be drawn from the questionnaires in upcoming clinical trials.

INTRODUCTION

Tinnitus is a phantom auditory perception in the absence of an external acoustic stimulus; a chronic and disabling disease. It can have a large impact on the quality of life experienced by the patient (Coles 1984; Davis and Rafaie 2000). Tinnitus is difficult to assess because it is a subjective symptom. Currently there are no accurate objective measurement options available. The subjective perceived Quality of Life by tinnitus patients is often evaluated using Health-Related Quality of Life (HR-QoL) questionnaires. Over time, many different disease specific HR-QoL instruments have been developed to measure the tinnitus burden, e.g., the Tinnitus Questionnaire (TQ), Tinnitus Handicap Questionnaire (THQ) and Tinnitus Handicap Inventory (THI) (Hallam et al. 1988; Kuk et al. 1990; Newman et al. 1996).

These questionnaires are commonly used in clinical practice, particularly to discriminate between patients and validated as such. Further, these instruments are increasingly used as an outcome measure in clinical trials; no consensus has been reached regarding which HR-QoL questionnaire is most powerful for this purpose. To be useful in clinical trials, validation regarding the responsiveness, i.e., the ability of the instrument to detect clinically important changes in HR-QoL over time, is also very important. An instrument should be able to detect at least that amount of change that patients experience as important. This responsiveness is essential for outcome measures (Kimberlin and Winterstein 2008).

This systematic review presents the different HR-QoL instruments currently used in clinical trials measuring effects of tinnitus therapy. For each of the instruments identified, its characteristics and validation details are reported.

MATERIALS AND METHODS

Search strategy

The bibliographic databases PubMed (1966-March 2009) and Embase (1988-March 2009) were searched using the terms *tinnitus*, *therapy* (clinical query)*, quality of life questionnaire*, and their synonyms to identify all randomized-controlled clinical trials on tinnitus treatment measuring HR-QoL, (see Table 1). In addition, a reference and related article search was performed.

Table 1 PubMed and Embase Search strategy

Search term	PubMed	Embase (only)
Tinnitus	Tinnitus	Tinnitus/exp
AND		
Therapy	Clinical query, broad	Therapy/exp
AND		
Questionnaire	Questionnaire OR Questionnaires OR Score OR Scale OR Index OR Inventory OR THI OR TQ OR THQ OR TSI OR TRQ	Questionnaire/exp
OR		
Quality of life	Quality of life OR Health status OR Functional Health Status	Quality of life/exp

Search in PubMed entering words as free text words or corresponding MeSH terms.
Limits: English language.

Study selection

Two reviewers independently screened identified titles and abstracts without blinding to authorship or journal. Potentially relevant studies were obtained and the full text examined. Discrepancies between reviewers were resolved by discussion. Criteria for inclusion were: tinnitus patients and evaluation of treatment with HR-QoL questionnaire. Studies were excluded if the study population consisted of specific patient groups (e.g. Menière's disease), patients with co-morbidity (e.g. hypertension), or patients with tinnitus as a symptom of another disease (e.g. acoustic neurinoma). Studies were also excluded if HR-QoL outcomes (means and standard deviations) were not reported for both the patient and control groups.

For each identified HR-QoL questionnaires, we subsequently searched for the published details regarding its test characteristics.

Data extraction

Information was gathered for each study on design, study population, number of included patients, type of intervention, duration of this intervention, and HR-QoL questionnaire used.

From the papers on the test characteristics we extracted the following psychometric information: number of items, scaling, range of scale, number of domains, constructs validity, internal consistency, reproducibility, and responsiveness.

RESULTS

Initially, 439 articles were identified with PubMed, whereas Embase revealed 205 studies that were not found by PubMed. Of these 644 studies, only 17 articles met the inclusion criteria.

The 17 unique studies (Andersson et al. 2002; Andersson et al. 2005; Bakhshaee et al. 2008; Ghossaini et al. 2004; Henry et al. 2007; Kaldo et al. 2007; Kroner-Herwig et al. 2003; Langguth et al. 2007; Mazurek et al. 2009; Mirz et al. 1999; Piccirillo et al. 2007; Rejali et al. 2004; Rief et al. 2005; Robinson et al. 2005; Rosenberg et al. 1998; Westerberg et al. 1996; Zoger et al. 2006) are listed in Table 2 with respect to the therapies evaluated and the questionnaire used. The number of patients studied varied between 10 and 269. Furthermore, different control groups were used, i.e., other forms of psychological counseling or cognitive behavior, patients on the waiting list, and placebo controls. In general, large variations in means and standard deviations were found between studies, and most placebo controlled trials reported large placebo effects (Mirz et al. 1999; Piccirillo et al. 2007).

Table 2 Overview of studies measuring HR-QoL to evaluate treatment outcome in tinnitus patients

Authors	Therapy	Instrument
Mirz et al	Low power laser through external acoustic meatus	THI
Piccirillo et al	Gabapentin	THI
Ghossaini et al	Electromagnetic therapy	THI
Kaldo et al	Cognitive behavioral treatment	TH, TRQI
Rejali et al	Ginkgo Biloba	THI
Rosenberg et al	Melatonin	THI
Westerberg et al	Baclofen	THI
Kroner-Herwig et al	Tinnitus coping training	TQ
Langguth et al	Active rTMS	TQ
Rief et al	Psychophysiologic intervention	TQ
Bakhshaee et al	Gabapentin	TQ
Andersson et al	Internet based Cognitive behavioral treatment	TRQ
Andersson et al	Cognitive behavioral treatment	TRQ
Henry et al	Educational group counseling	TSI
Robinson et al	Paroxetin	THQ
Zoger et al	Sertralin	TSQ

THI=Tinnitus Handicap Inventory, TQ = Tinnitus Questionnaire, TRQ = Tinnitus Reaction Questionnaire, TSI = Tinnitus Severity Index, THQ = Tinnitus Handicap Questionnaire, TSQ = Tinnitus Severity Questionnaire

Six different HR-QoL questionnaires were used in the 17 included studies: the Tinnitus Handicap Inventory (THI) in seven studies (Ghossaini et al. 2004; Kaldo et al. 2007; Mirz et al. 1999; Piccirillo et al. 2007; Rejali et al. 2004; Rosenberg et al. 1998; Westerberg et al. 1996), the Tinnitus Questionnaire (TQ) in five studies (Bakhshaee et al. 2008; Kroner-Herwig et al. 2003; Langguth et al. 2007; Mazurek et al. 2009; Rief et al. 2005), the Tinnitus Reaction Questionnaire (TRQ) in three studies (Andersson et al. 2002; Andersson et al. 2005; Kaldo et al. 2007), the Tinnitus Severity Index (TSI) in two studies (Bakhshaee et al. 2008; Henry et al. 2007), the Tinnitus Handicap Questionnaire (THQ) in one study (Robinson et al. 2005), and the Tinnitus Severity Questionnaire in one study (Zoger et al. 2006). Two studies used two different questionnaires simultaneously, i.e., THI/TRQ and TQ/TSI HR-QoL (Bakhshaee et al. 2008; Kaldo et al. 2007).

The test characteristics of the six HR-QoL questionnaires (Coles RRA et al. 1992; Hallam et al. 1988; Kuk et al. 1990; Meikle et al. 1995; Newman et al. 1996; Wilson et al. 1991) are presented in Table 3. All instruments measure disease-specific HR-QoL, i.e., the tinnitus burden. The shortest instruments are the TSI and TSQ, with 12 and 10 items, respectively, whereas the TQ has 52 items covering six domains. All questionnaires, with exception of the THQ, use ordinal scales for each item. In the THQ, the patients score the percentage they agree with the item (0-100%).

Table 3 Characteristics of HR-QoL instruments used to evaluate outcome

Instrument	Items	Score	Range	Domains
THI	25 items	0 – 2 – 4 (0) never, (2) sometimes, (4) yes	0 – 100	Three domains: Functional, emotional, catastrophic responses
TQ	52 items	True, partly true, not true	0 – 84	Six domains: Emotional distress, cognitive distress, intrusiveness, auditory perceptual difficulties, sleep disturbance, somatic complaints
TRQ	26 items	0 – 4 (0) not at all – (4) almost all of the time	0 – 104	Four domains: General distress, interference, severity, avoidance
TSI	12 items	0 – 4 (0) never – (4) always	0 – 48	No domains
THQ	26 items	0 – 100 (0) strongly disagree – (100) strongly agree	0 – 2700	Three domains: Physical health/emotional status/ social consequences, hearing and communication, personal viewpoint
TSQ	10 items	0 – 4 (0) not affected – (4) always affected	0 – 40	No domains

THI=Tinnitus Handicap Inventory, TQ = Tinnitus Questionnaire, TRQ = Tinnitus Reaction Questionnaire, TSI = Tinnitus Severity Index, THQ = Tinnitus Handicap Questionnaire, TSQ = Tinnitus Severity Questionnaire

The psychometric characteristics (construct validity, internal consistency, reproducibility and responsiveness) of each of the six HR-QoL questionnaires are given in Table 4. The construct validity, which examines the extent to which the concepts of interests are comprehensively represented by the items in the questionnaire (Guyatt et al. 1997; Kirshner and Guyatt 1985; Terwee et al. 2007; Testa and Nackley 1994), is good for four of the six questionnaires. For the TSI and TSQ the construct validity has not been assessed.

The internal consistency, which measures the correlation between the different items in the instrument (Guyatt et al. 1997; Kirshner and Guyatt 1985; Terwee et al. 2007; Testa and Nackley 1994), for which the Cronbach's α is mostly used, was higher than 0.9 for five HR-QoL instruments, but the subscales of the THQ and THI lack internal consistency. The internal consistency of the TSQ is unknown. The reproducibility, which is the ability to reproduce the same results when nothing has changed (Guyatt et al. 1997; Kirshner and Guyatt 1985; Terwee et al. 2007; Testa and Nackley 1994), was high (>0.8) for all instruments. Responsiveness, which measures the ability to detect a clinically important change over time, was not reported for any of the six instruments.

Table 4 Psychometrics of identified HR-QoL instruments

Instrument	Construct validity	Internal consistency (Cronbach's α)	Reproducibility (test re-test)	Responsiveness
THI	+	0.93 (subscales: 0.56-0.87)	0.92	-
TQ	+	0.95	0.94 (subscales 0.86-0.93)	-
TRQ	+	0.96	0.88	-
TSI	-	0.92	0.88	-
THQ	+	0.94 (subscales: 0.47-0.95)	0.88	-
TSQ	-	-	-	-

THI=Tinnitus Handicap Inventory, TQ = Tinnitus Questionnaire, TRQ = Tinnitus Reaction Questionnaire, TSI = Tinnitus Severity Index, THQ = Tinnitus Handicap Questionnaire, TSQ = Tinnitus Severity Questionnaire
+ = Validated, positive,- = Not validated

DISCUSSION

This review identified six different HR-QoL instruments that are currently used to measure treatment outcomes in tinnitus trials. All instruments were only validated for discriminative use. None of them were validated for evaluative purposes, which is necessary to be useful in clinical trials. To our knowledge, we are the first to present an overview of the HR-QoL questionnaires currently used to measure outcome in clinical trials and list their psychometric properties. On the other hand, publication bias cannot be precluded, i.e., articles presenting (negative) data on responsiveness might not have been published. Several experts in the field, however, were asked their opinion on this issue, and their general response was that the responsiveness factor has indeed not been studied yet.

Validation of test responsiveness is necessary to optimize the usefulness of these HR-QoL instruments in tinnitus trials. Responsiveness is the ability of a measure to detect change over time in the construct of interest. For outcome measures intended to evaluate the effects of medical or educational interventions, responsiveness to changes that result from the intervention is required. Reliability is a crucial component of responsiveness. The "noise" that is due to measurement error can mask changes that may, in fact, be attributable to the intervention. A new disease-specific quality-of-life instrument that has not demonstrated stability over time when there is no change in health status (which may be an indication of measurement error) may not be able to detect health status changes. Furthermore, measures that have ceiling effects have a limited ability to assess positive changes that may result from the intervention, because there is limited room for subjects to improve their scores. Responsiveness to change can legitimately differ from one population to another, which is why the measure must be appropriate to the subjects being studied (Kimberlin and Winterstein 2008). Only when the responsiveness of a questionnaire is validated can an HR-QOL instrument be used to study the effectiveness of different interventions.

The Tinnitus Research Consortium is currently validating a new questionnaire, the Tinnitus Functional Index, which was specifically developed to measure treatment outcome (Snow 2006). The psychometric quantities of this new questionnaire should be compared with those of the questionnaires that are already available. Recommendation should be made as to which questionnaire can best be used to optimize treatment evaluations. Future clinical studies on tinnitus will benefit from such recommendations since it will enable better comparisons between such trials and subsequently increase the possibilities of meta-analyses in this field.

In conclusion, the disease-specific HR-QoL instruments used in clinical trials on tinnitus appear not to be validated to measure the effectiveness of intervention therapies and, therefore, should not be used as such.

The validity, reliability, and responsiveness of each tinnitus-specific HR-QoL should be studied before final conclusions can be drawn regarding the utility of these questionnaires in future clinical studies.

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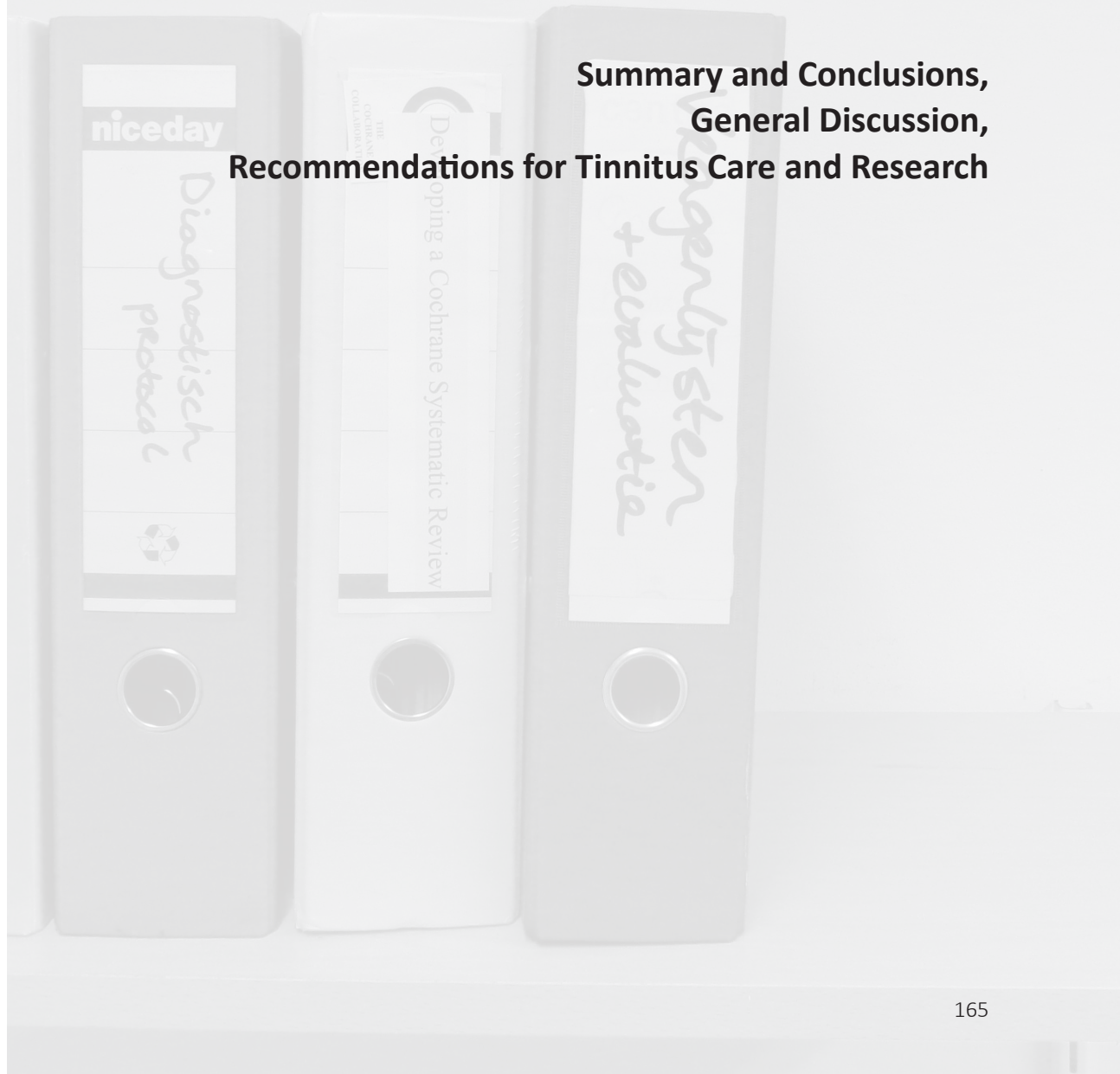
Chapter 8

Summary and Conclusions, General Discussion, Recommendations for Tinnitus Care and Research



SUMMARY AND CONCLUSIONS

In this thesis diagnostic and therapeutic aspects of tinnitus are assessed, based on the notion that tinnitus most probably arises from hyperactivity in the central nervous system. Between June 2007 and November 2012 three-hundred-twenty-one patients have been evaluated by the Tinnitus Care Group of the University Medical Center Utrecht (UMC Utrecht). At this Tinnitus Care Group patients are assessed through a structured diagnostic protocol and evaluated by a multidisciplinary team. The content of this diagnostic protocol and the 321 patients that were seen during this period are described in chapter two. Patient experiences and tinnitus burden (on the Tinnitus Handicap Inventory) were assessed three months after their visit. Patients were generally satisfied with the care they had received and the burden of their tinnitus was slightly, but significantly lower. A larger significant effect was obtained by the - newly in our clinic offered - Tinnitus Tips and Tricks group course.

Tinnitus is a highly prevalent symptom with potential severe morbidity. Fortunately, only a small proportion of the population experiences problems due to their tinnitus in such a degree, that it influences their quality of life negatively. It is not known why these individuals develop more burden from tinnitus. In chapter three socio-demographic, health, and tinnitus factors potentially related to tinnitus severity were investigated. It was shown that a higher percentage of tinnitus awareness during the day, existence of self-reported depression and/or anxiety, higher education, existence of additional somatic complaints, louder tinnitus (subjectively experienced), and more variable tinnitus in loudness and/or pitch (subjectively experienced) were related to more severe tinnitus. Awareness during the day turned out to be the most important factor.

Magnetic Resonance Imaging (MRI) might be helpful to diagnose the cause of tinnitus. Different recommendations on the use of MRI in tinnitus diagnosis have been made previously and the usefulness of a routine MRI scan remained uncertain. A routine MRI scan in tinnitus patients could be useful to exclude a vestibular schwannoma or to find serious but less prevalent conditions causing tinnitus. Opposing routine MRI scanning are financial costs and the fact that it leads to incidental, non significant findings, which could lead to unnecessary patient's concerns. A potential uncertainty that may arise from routine MRI scanning is the clinical relevance of a vascular loop of the Anterior Inferior Cerebellar Artery (AICA) in relation to a possible audiovestibular nerve compression syndrome. In chapter four the diagnostic yield of a routine MRI scan in chronic tinnitus patients was assessed and the frequency of incidental findings was defined. It was shown that a routine MRI scan is of little or no value in tinnitus patients with persistent complaints, both in bilateral as well as in unilateral tinnitus patients. Incidental findings were common. AICA loops were often encountered on

an MRI scan, but rarely relate to the tinnitus. When looking at the diagnostic criteria for cochleovestibular nerve compression syndrome proposed by the Tinnitus Research Initiative (www.tinnitusresearch.org) a definite syndrome was only shown in three patients (4.3%). AICA loops that are found on an MRI scan should thus be considered incidental findings, unless the syndrome was suspected beforehand on clinical grounds and the MRI scan was made specifically to diagnose or exclude this syndrome.

If tinnitus originates from hyperactivity in the central nervous system, anticonvulsant medication seems a plausible treatment for tinnitus. In chapter five a Cochrane review is described including seven trials on four different anticonvulsants (gabapentin, carbamazepine, lamotrigine and flunarizine). Most of the studies included in the review have a moderate or high risk of bias as descriptions of the methodologies that were used are minimal. There is no evidence from studies performed so far that these anticonvulsants have a large positive effect in the treatment of tinnitus, but a small effect (of doubtful clinical significance) has been demonstrated.

In chapter six a randomized controlled (RCT) trial on the effect of repetitive Transcranial Magnetic Stimulation (rTMS) is described. rTMS at a low-frequency stimulation rate can cause inhibition, again a plausible therapy against the central nervous system's hyperactivity. Fifty chronic tinnitus patients who had been seen at the Tinnitus Care Group of the UMC Utrecht were included in the study. It was shown that low-frequency rTMS was not effective in treating tinnitus. Although other studies (patient series and cross-over studies) have shown positive trends in favor of rTMS, the found effects are so small that they should be considered clinically irrelevant. Untill now four RCTs have been performed. Two do not show an effect of rTMS either, while two other studies do show an effect. Though it seems that low-frequency rTMS has been adequately shown not to be effective in the general population of tinnitus patients, it remains debatable if rTMS might be effective in certain subgroups of patients or with stimulation at a different stimulation rate or another brain location. Considering the found effect in two parallel RCTs stimulating their patients at the temporoparietal junction, this might be a more effective target for rTMS than the auditory cortex specifically. In the present study it was shown that there was a trend for a slightly larger improvement after rTMS, albeit clinically still small, in patients with a higher degree of burden.

A difficulty in therapeutic tinnitus research is that there is no universally accepted tinnitus outcome parameter. Different tinnitus-specific questionnaires are used to measure treatment effects and a review on these questionnaires is presented in chapter seven. This review identified six different Health-Related Quality of Life instruments that are currently used to measure treatment outcomes in tinnitus trials: the Tinnitus Handicap Inventory, the Tinnitus Questionnaire, the Tinnitus Reaction Questionnaire, the Tinnitus Severity Index, the Tinnitus Handicap Questionnaire, and the Tinnitus Severity Questionnaire. It was shown that none of these questionnaires is validated to measure the effectiveness of intervention therapies.

GENERAL DISCUSSION

In this section we reflect on the validity and reliability of the main findings in the different chapters of this thesis. Per chapter we will discuss whether or not bias or reliability issues (selection bias, measurement bias, and confounding) may be applicable to the main findings.

In chapter three socio-demographic, health and tinnitus factors potentially related to tinnitus severity were investigated in three-hundred-and-nine patients. All these patients were seen at the Tinnitus Care Group of the UMC Utrecht. The design of the Tinnitus Care Group only allowed patients who were referred by an ear, nose and throat specialist or an audiologist to be seen at the Tinnitus Care Group directly. Patients referred by a general practitioner were planned to be first assessed at the general outpatient clinic, but sometimes these patients were assessed directly by the Tinnitus Care Group as well. This design entails a form of selection bias. It would probably lead to inclusion of mainly tinnitus patients with persistent complaints and/or without an adequate diagnosis (patients at which the Tinnitus Care Group was aimed at helping). We do not believe this selection bias influences our findings in chapter three, though. We intended to investigate which factors are related to tinnitus burden. To reliably answer this question many patients are needed with different levels of tinnitus severity. As explained in chapter three the patients included in this study experienced severity on all levels as measured with the questionnaires, thus the possible selection bias does not seem to hinder the aim of this chapter. In tinnitus research the potential of measurement bias forms a plausible risk. No tinnitus-specific questionnaire, Visual Analogue Scale or Likert scale is universally accepted as the best measurement of tinnitus severity. To (partially) correct for this potential form of bias we included two tinnitus-specific questionnaires as outcome measurement for tinnitus severity. We believe this verification to be reliable because three of the six contributing factors were found on both questionnaires. The additional three factors were found to contribute on only one of the two questionnaires, but these factors were among the first to be excluded from the analysis on the other questionnaire. Thus, the two questionnaires used in this study measure severity broadly similar. Potential confounding was a real threat in this study, because little was known of potentially contributing factors. To correct for possible confounding factors we decided to include as many factors as possible, while respecting the 10:1 ratio criterion for the required number of participants per factor for reliable outcomes of the analyses. This 10:1 ratio was adequately reached in the study (309 participants to 28 factors). Secondly, we analyzed the univariate effects according to three domains and for all domains a higher than 15:1 ratio for participants per factors is obtained. Subsequently only factors with a univariate effect were entered in the multivariate analyses.

Therefore, this study included sufficient participants to draw reliable conclusions from. Because many analyses were performed which poses a risk for finding accidental correlations, verification through correction for multiple comparisons was performed, showing that all factors that resulted from the multivariate analyses retained significance.

The most important risk of bias for chapter four is the risk of selection bias. This chapter studies the diagnostic yield of a routine MRI scan. Risk of selection bias is high because the study includes only patients that were seen in a tertiary tinnitus clinic. Patients had generally already been seen by an otorhinolaryngologist or an audiologist in the past and had sometimes undergone different forms of investigation. It is possible that some of these patients had already had an MRI scan previously. This scan would then have most probably been without relevant abnormalities, otherwise it would have been unlikely that the patient would have been presented to our clinic. It is therefore plausible that there is an underestimation of abnormalities related to tinnitus in our population compared to a population of tinnitus patients that would be scanned at their primary visit. So, care should be taken to extrapolate our results to a general tinnitus population. Considering the low number of related abnormalities found in this study, it seems likely that the yield of a standard MRI scan would be too low in such a population as well. A second risk of bias in this study is the risk of measurement bias. MRI scans were assessed by different radiologists. On the other hand this gives an adequate view of the standard diagnostic process, which allows to more reliably generalize the results of this study to the common practice. Potential confounding could play an important role in the question of the diagnostic yield of a routine MRI scan because there would be no definite proof for the relationship between the potentially found abnormality and the tinnitus. However, because in this study the diagnostic yield was very low (in only seven patients an abnormality possibly related to the patient's tinnitus was found) this potential confounding will not have influenced the conclusions.

The question of potential bias causing factors can be posed on two levels for chapter five. In this chapter the effect of anticonvulsants is studied by performing a Cochrane review. In the first place potential bias causing factors (in the sequence generation, allocation concealment, blinding, incomplete outcome data availability, selective outcome reporting and other forms of biases) may be identified in the individual included studies itself. As explained in chapter five, indeed, the overall risk of bias of the included studies was "high" or "unclear". This was mainly so because studies included minimal information on their methodology. High risk of bias was mostly seen because of failure to report incomplete outcome data. Unclear risk of bias was often seen in the selection and blinding process. Secondly, potential bias causing factors may be identified in the review process. Potential selection bias in the included studies was minimal as the search for studies was performed by the Cochrane Collaboration which has very extensive experience with finding studies. Further selection of studies was performed independently by two authors and data extraction independently by

three authors. In this chapter the potential of measurement bias may play a role. As explained in chapter seven, none of the questionnaires used in therapeutic trials are validated to measure effectiveness of intervention therapies. Secondly, no questionnaire is universally accepted and therefore comparison between studies is hindered. We lowered this chance by including self-assessment scales as outcome measurement, in addition to the tinnitus specific questionnaires which we had defined to be our primary outcome measurement. This did not change the conclusions. The meta-analysis was definitely hindered though by the fact that the included studies used different outcome measurements. Potential confounding factors in the review process were not identified.

In chapter six the effect of rTMS was studied in fifty patients that had been seen at the Tinnitus Care Group of the UMC Utrecht. All patients who had been seen at the Tinnitus Care Group were considered for inclusion and no base for selection bias can be identified. The study intended to investigate the effect of rTMS in patients with tinnitus burden, therefore no role of the fact that patients came from a tertiary tinnitus clinic in potential bias can be seen. As explained before (with respect to chapter five), also for this chapter the potential of measurement bias may play a role. This was recognized beforehand and to correct for this potential form of bias three different outcome measurements were included in the study. There is no reason to believe that confounding was an issue in this study. Subgroup analyses were performed in all areas that could potentially influence the effect of rTMS. Only for the group of tinnitus patients with more severe tinnitus a trend for a better effect was observed. However, this effect was too small to be deemed clinically relevant. Therefore there is no reason to believe that the results of this study are influenced by confounding factors in the characteristics of the study population.

Because chapter seven is a review like chapter five, the question of potential bias causing factors can be posed on two levels here as well. This chapter reviews the different tinnitus-specific questionnaires that are used to measure treatment effects in tinnitus trials. In the first place potential bias causing factors may be identified in the individual included studies itself. Because only the information on which questionnaire was used as outcome measure, was extracted from these studies, the question of potential bias within these studies is not eminent. Secondly, potential bias causing factors may be identified in the review process itself. Potential selection bias in the included studies was minimal as the search for studies was quite broad and further selection of studies was performed independently by two authors. Measurement bias and confounding in the review process were not an issue. This review gave only an overview of the questionnaires used and their psychometric characteristics, no new analyses were performed.

RECOMMENDATIONS FOR TINNITUS CARE

In this section we reflect on recommendations for tinnitus care based on the insights gained through this thesis and based on personal experiences gained at the Tinnitus Care Group and general outpatient clinics.

The first and foremost important step in tinnitus care is assessing the patient's reason for contacting a physician. There are different reasons why a patient may decide to go to a physician for their tinnitus. Patients have different needs, they may desire only an explanation on the cause of their tinnitus, may wish information on possible therapies or lack thereof or may be in need of help because of high distress. Time should be taken to first assess the patient's needs and care should be taken not to jump to conclusions on this subject to prevent the patient leaving the visit dissatisfied. Approximately ten percent of patients that were assessed by our Tinnitus Care Group experienced no or hardly any burden from their tinnitus and should therefore not have been referred to our Tinnitus Care Group. Especially, because focusing attention on tinnitus (which visiting the Tinnitus Care Group could lead to for patients with hardly or no burden) might form a risk for developing higher burden. Adequate explanation in an early stage would have probably satisfied their needs. It seems likely that in this early stage the need of the patient was not adequately assessed before the patient was referred to our Tinnitus Care Group. A second option is that their burden had diminished while being on the waiting list for the Tinnitus Care Group.

Physical examination should include otoscopy as part of the diagnostics for the potential otologic cause of tinnitus in all patients. Auscultation should be performed when a somatosound is expected. Audiometry should be routinely performed in tinnitus patients to diagnose the potential cause of the tinnitus. Pitch and loudness matching can be performed to estimate the potential benefit of a hearing and/or masking aid. There is no role for routine imaging as was shown in this thesis (chapter 4). An MRI scan should be performed when on other clinical grounds a specific cause, with tinnitus as possible symptom, is expected (e.g. a vestibular schwannoma based on audiometric tests). When a patient hears a pulse-synchronous pulsatile sound Magnetic Resonance Angiography should be considered to exclude a diagnosis for a somatosound.

In advising the patient on therapy a stepwise approach seems wise (see Figure 1). The sequence of these steps is simplified to a sequence that would be logical in most tinnitus patients. However, this sequence should be evaluated in each patient and individual deviations to this sequence are to be expected. Tailored information (depending on the patient's needs) on the cause and pathophysiology of tinnitus and potential therapeutic options (e.g. hearing

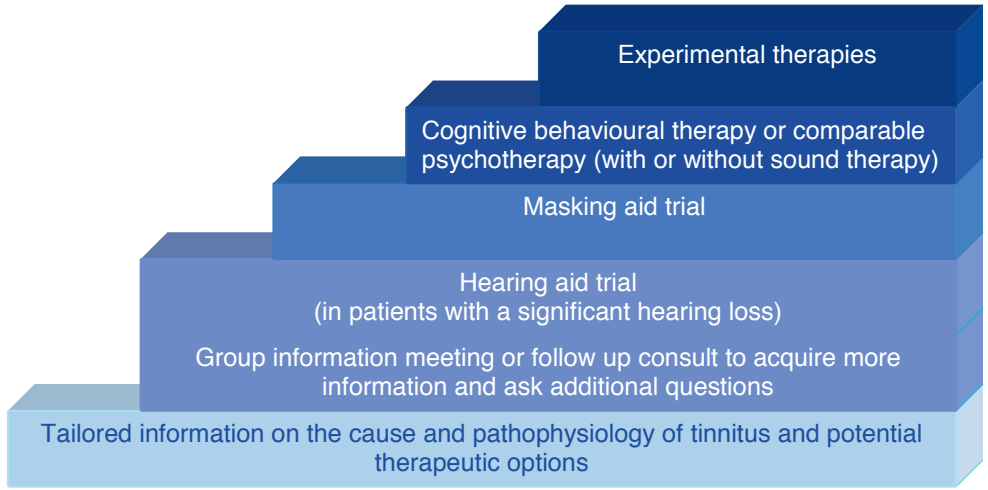


Figure 1 Stepwise approach tinnitus care

or masking aid, cognitive behavioral therapy (CBT) or treatment of depression) should be discussed with all patients. When hardly any or no burden is experienced by the patient (experimental) therapies should be discouraged and it should be explained that these could lead to more attention to the tinnitus and subsequently a risk for developing (higher) burden. If no therapy is started a patient should explicitly be offered the option of returning for a second visit if new questions come up or higher burden develops. Patients should receive a well-designed brochure on tinnitus so that they can re-evaluate the information that they have been given. For patients requesting more information, instead of individual follow-up visits, a regular group information meeting as a second step can be considered at which patients can acquire more information on tinnitus and ask questions to peers and counselors. In tinnitus patients with a significant hearing loss as an additional option in the second step the use of hearing aids can be tried in the large proportion of these patients (Del Bo and Ambrosetti 2007). As a third step masking devices can be tried (in combination with a hearing aid in case of significant hearing loss). If still in need, as a fourth step the patient can be offered cognitive behavioral therapy (CBT) or a comparable psychotherapy, in combination with sound therapy or not. CBT has been proven to be effective in lowering of the tinnitus severity (Martinez-Devesa et al. 2010). As a last step therapies that are deemed experimental because no adequate proof of their (in)effectiveness is available, can be considered. The pros en cons and the unknown effects of these experimental therapies should be discussed well with the patient. Medication therapies should be seen as such experimental therapies. This thesis (chapter 5) shows in a review of low-quality trials that anticonvulsants may have a small effect (of doubtful clinical significance). For antidepressants there is insufficient evidence from low-quality trials that they improve tinnitus (Baldo et al. 2006). Patients with

concomitant depression and/or anxiety problems should always be referred to a psychiatrist for the treatment of these disorders, while the stepwise approach to the tinnitus should be followed in parallel.

With this stepwise approach it is hoped that both a higher patient satisfaction and a lower amount of doctor contacts (2nd and 3rd opinions) and thus lower health care costs is reached. In this thesis (chapter 2) it was shown that patients are generally satisfied by the Tinnitus Care Group and they specifically mention to appreciate that they had been heard and that they had gained a better insight in their tinnitus. This highlights the importance of our proposed first step. Also we were able to show that following of the diagnostic protocol alone lowered their tinnitus severity slightly, but significantly.

RECOMMENDATIONS FOR TINNITUS RESEARCH

Because many questions remain on the pathophysiology of tinnitus, continuing research in this area is important. An important question that remains is why some of the symptomatic patients develop more burden, while most of them do not. This thesis shows demographic-, health-, and tinnitus-related factors that are associated with more burden (chapter 3). Imaging studies in the form of voxel based morphometry and functional MRI comparing patients with and without much burden could give answers on the structural and functional brain changes that occur in patients who have developed burden. If successful, these imaging options might be used as the long sought for method to objectively assess the severity of tinnitus.

This thesis shows that low-frequency rTMS is not effective in treating chronic tinnitus (chapter 6). Anticonvulsants as well, are shown in this thesis to be at least not very effective (chapter 5). There is no reason to believe, though, that there is no therapy that would be effective in treating tinnitus. Research on potential therapies should therefore be continued in all potential areas. It should be realized, though, that tinnitus is a very diverse symptom and that different subgroups of patients might exist that could respond differently to different therapies. It is therefore advised that therapeutic research be only performed in large enough study populations so that subgroup analyses could be performed or that research should be performed in well-defined subgroups. The latter being difficult, because in general it is not known of what patient (characteristics) these subgroups exist. Many proposals and thoughts on tinnitus subgroups have been made, but no definite proof for relationships between certain subgroups and treatment effects is presently available.

This thesis shows (chapter 7) that until recently there was no outcome parameter which was validated to measure the effectiveness of intervention therapies. In 2012 the Tinnitus Functional Index (TFI) was published (Meikle et al. 2012). This questionnaire was specifically designed to measure treatment-related changes in tinnitus. The nine existing tinnitus-specific questionnaires (Tinnitus Handicap Inventory, the Tinnitus Questionnaire, the Tinnitus Reaction Questionnaire, the Tinnitus Severity Index, the Tinnitus Handicap Questionnaire, the Tinnitus Severity Scale, the Tinnitus Severity Grading, Subjective Tinnitus Severity Scale, and Tinnitus Retraining Therapy Initial Interview) were used as the primary starting point for the item selection of the TFI and thus there is content overlap between the TFI and these other questionnaires. It seems that this questionnaire succeeds well in measuring changes as it was shown that the responsiveness in patients that have improved is high (Cohen's d effect size of 0.84 – 1.47 after 3 and 6 months, which reflects are large clinically relevant difference), while the responsiveness in patients with unchanged tinnitus is low (Cohen's d effect size of 0.14 – 0.15 after 3 and 6 months, which reflects a negligible

difference). Because this questionnaire has only recently been published, more definite evidence from future studies about the relative responsiveness is required. Because it seems to be an adequate questionnaire to measure treatment effects it is advised to include this measure as outcome measure, in addition to at least one or two other tinnitus-specific questionnaires, VAS or Likert scales so that comparability with existing studies is retained. The Tinnitus Questionnaire and the Tinnitus Handicap Inventory are used most often and are therefore preferred.

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Appendix

Nederlandse Samenvatting

Dankwoord

Publications

About the Author

Appendix

Patients' original answers in Dutch to the question: "How did you experience your visit to the Tinnitus Care Group?"

Plezierig, deskundige artsen en audioloog. Met name gesprek met psycholoog was erg plezierig.
Zwaar
Goed, er is alle tijd voor genomen en goede uitleg, er wordt aandacht aan besteed
Goed, iedereen heel aardig, afspraken op tijd. Eindgesprek met 4 doktoren beetje veel
Prettig, zorgvuldig, zinvol. Wel gaat er af en toe wat fout bij het maken van afspraken.
Prettig en professioneel. Ondanks het feit dat er geen oplossing is voor mijn probleem toch het gevoel dat ik serieus ben geholpen!!
Normaal, geen bijzonderheden
Hulp van audioloog (gesprek was nuttig) daar werd ik goed door gerustgesteld. Psycholoog ook goed. MRI was goed. Specialist vertelde mij te weinig, vertelde niet wat hij dacht, waarom hij onderzoek deed
Positief
Met goed gevoel
Goed
Goed, de dame die de gehoortest afneemt de laatste 2 keer is erg aardig en behulpzaam!
Goede evaluatieformulieren
Daar ben ik tevreden over. Ik voelde mij serieus genomen. Men begreep mijn klachten. Nam de tijd voor het onderzoek
Ondanks dat de ruis soms erger is ben ik dankbaar dat ik alle vragen in moest vullen. Mijn zelfvertrouwen is wat teruggekomen en ook dat er naar me geluisterd is. Ik durfde niet meer te bellen of met vreemde mensen te praten. Ik dank u allen
Doordat ik alle lijsten zelf in moest vullen heb ik meer eigenwaarde terug gekregen
Positief, maar ook heftig
Zeer goed
Goed
Slecht omdat ik niet goed geholpen ben mijn gehoor is achteruit gegaan het oorsuizen daar hebben ze niks aan gedaan ik zit er nog steeds mee
Positief
Goed om een keer door de mangel te worden gehaald, maar de uitkomst was (zoals verwacht) teleurstellend

Deze heb ik als prettig ervaren
Zorg goed alleen te veel afspraken op verschillende dagen.
Goed met dien verstande dat ik achteraf onverantwoord vind om mijn een MRI scan te laten ondergaan, waarbij ik slechts oordopjes mocht dragen en terwijl de MRI tot wel 140dB aan geluid produceert. Mijn tinnitus komt namelijk voort uit een geluidstrauma en daarvoor hem ik met de dokter gesproken. Ik heb uiteindelijk blijvende verergering van mijn tinnitus klachten overgehouden.
Uitgebreid, zorgvuldig, realistisch
Goed
Plezierig
Goed!
Bijzonder prettig. Goede ontvangst, goede informatie. Goed georganiseerd
Goed - prima begeleiding - zorgzaam
Prettig
Er goed, het gaf me inzicht in waar mijn klachten vandaan kwamen en daardoor enigszins gerust gesteld. Het was uitgebreider dan gedacht!
Prettig, werd serieus genomen
Luisterend oor. Ze hebben mijn zo goed mogelijk geholpen. Werd serieus genomen. Ik had wel gehoopt dat het ruisen beter onder controle kon worden gebracht, en dat is jammer
Verhelderend, geruststellend, informatief erg goed
Zeer goede ervaring en ben zeer blij met de vervolg cursus.
Zeer prettig
Positief: eindelijk aandacht voor dit ellendige probleem. Helaas geen oplossing al werd dat wel op tv gesuggereerd door een audioloog
Goed
Prettig
Het had me niet gebracht waar ik op had gehoopt. Ik bedoel, ik had het liefst een operatie of een pil, zodat ik het niet meer kan horen! Maar ja…. Wellicht komt er nog iets op de markt wat werkt!
Uitstekend!! Er is echt aandacht en zorg aan mijn problemen met tinnitus besteed. Hierdoor kan ik er veel beter mee omgaan!!
Als zeer positief en leerzaam
Erg positief. De afhandeling minder / vervolgstappen onduidelijk
Goed
Duidelijk en zinvol
Goed, begripvolle artsen en medewerkers
Prima

Voldoende aandacht. Wat minder aandacht bijkomende gehoorproblemen zoals post nasal drip en hyperacusis en medicijngebruik
Goed
Bezoek voor analyse goed. Verder zie bijschrift (niet aanwezig)
Zeer professioneel, uitgebreid onderzoek, klacht is serieus genomen
Goed
Prettig. Het heeft me inzicht in tinnitus geboden en mijn ongerustheid tav ernstige ziektes weggenomen. De reguliere geneeskunst kan weinig voor me doen.
Zeer prettig en deskundig personeel die begrepen welke problemen ik heb met mijn gehoor
Positief, alles werd uitgebreid onderzocht. Geruststelling dat er niets ernstig aan de hand was.
Negatief, volgens psycholoog zat het tussen mijn oren. Hier kan ik weinig mee.
Professioneel en keurig
Ook al ben ik er niet mee geholpen, vond ik het toch fijn dat ik bij jullie ben langs geweest. Ik probeer er nu mee te leven, de ene keer heb ik meer last van de geluiden en een andere keer minder.
Goed en slecht. Goed omdat ze wel luisteren en laten onderzoeken maar op 2de afspraak om recept te krijgen heb ik 5 maanden moeten wachten.
Zeer positief
Zeer positief, uitgebreid onderzoek en daarmee dingen uitgesloten. Belangrijk vond ik gesprekken/voorlichting met psycholoog.
Prettig; er werd gedegen onderzoek gedaan
Positief. Het geeft in ieder geval de hoop dat er verbetering kan optreden. En dat de tinnitus serieus wordt genomen. Hopelijk komt er nog een doorbraak!
Goed. Tevreden over de behandeling.
Zeer positief. Door alle tests weet ik nu dat het alleen aan mijn gehoor ligt en niet dat er wat anders aan de hand is.
Prettig
Fijn
Geruststellend
Goed, zinvol
Zeer positief
Professioneel
Goed
Goed
Heel goed

A

Nederlandse samenvatting

In dit proefschrift werden diagnostische en therapeutische aspecten van tinnitus onderzocht, gebaseerd op de gedachte dat tinnitus meest waarschijnlijk ontstaat door hyperactiviteit in het centraal zenuwstelsel (de hersenen). Tussen juni 2007 en november 2012 werden 321 tinnituspatiënten geëvalueerd door de Zorggroep Tinnitus van het Universitair Medisch Centrum Utrecht (UMC Utrecht). Bij deze Zorggroep Tinnitus worden patiënten onderzocht via een gestructureerd diagnostisch protocol en geëvalueerd door een multidisciplinair team. De inhoud van dit diagnostisch protocol en de karakteristieken van de patiënten die gezien zijn in deze periode, worden beschreven in hoofdstuk 2. Patiëntervaringen en de tinnituslast (gemeten op de Tinnitus Handicap Inventory) werden drie maanden na het bezoek aan de Zorggroep Tinnitus gemeten. Patiënten waren over het algemeen tevreden met de zorg die ze ontvangen hadden en hun tinnituslast was niet veel, maar wel significant, lager. Een groter effect lijkt behaald te kunnen worden met, een voor onze kliniek nieuwe behandeloptie, namelijk, de Tinnitus Tips en Trucs groepscursus.

Tinnitus is een veelvoorkomend symptoom met mogelijk ernstige morbiditeit. Gelukkig ervaart alleen een klein gedeelte van de populatie in die mate problemen van de tinnitus dat het hun kwaliteit van leven negatief beïnvloedt. Het is niet bekend waarom deze individuen meer last van hun tinnitus ontwikkelen. In hoofdstuk 3 werd onderzocht met welke sociaaldemographische, gezondheids-, en tinnitusfactoren tinnitusernst gerelateerd kan zijn. Een hoger percentage bewustheid van de tinnitus gedurende de dag, de aanwezigheid van zelfgerapporteerde angst en/of depressie, een hoger opleidingsniveau, de aanwezigheid van bijkomende somatische klachten, luidere tinnitus (subjectief ervaren) en meer variabele tinnitus in luidheid en/of toonhoogte (subjectief ervaren) bleken gerelateerd met (subjectief ervaren) tinnitusernst. Bewustheid van de tinnitus gedurende de dag bleek de belangrijkste factor.

Magnetic Resonance Imaging (MRI) zou kunnen bijdragen aan het stellen van de diagnose van de oorzaak van tinnitus. Verschillende aanbevelingen voor het gebruik van een MRI scan voor tinnitus diagnostiek zijn tot op heden gedaan, maar het eventuele nut van een routine MRI scan is onduidelijk. Een routine MRI scan bij tinnituspatiënten zou nuttig kunnen zijn om een vestibularis schwannoom uit te sluiten of om ernstige, maar minder voorkomende, oorzaken van tinnitus uit te sluiten. Financiële kosten en toevalsbevindingen die tot onnodige onzekerheid bij patiënten kunnen leiden, pleiten tegen routinematig scannen. Een mogelijke onzekerheid die door routinematig scannen zou kunnen ontstaan, is de klinische relevantie van de anterieure inferieure cerebellaire arterie (AICA) in relatie tot een mogelijk compressiesyndroom van de nervus vestibulocochlearis. In hoofdstuk 4 werd de

diagnostische opbrengst van een routine MRI scan bij chronische tinnituspatiënten onderzocht en werd de mate van toevalsbevindingen vastgesteld. Er werd gezien dat een routine MRI scan (bijna) geen waarde heeft, noch bij bilaterale noch bij unilaterale tinnituspatiënten. Toevalsbevindingen kwamen veel voor. AICA loops werden regelmatig op de MRI scan gezien, maar hadden nauwelijks relatie met tinnitus. Wanneer gekeken werd naar de diagnostische criteria voor het compressiesyndroom van de nervus vestibulocochlearis, voorgesteld door de Tinnitus Research Initiative (www.tinnitusresearch.org), werd een definitief syndroom bij slechts drie patiënten (4.3%) gezien. AICA loops die gezien worden op de MRI scan moeten dus als toevalsbevinding beschouwd worden, behalve wanneer dit compressiesyndroom op klinische gronden verdacht wordt en de MRI scan specifiek gemaakt wordt om dit syndroom te bevestigen cq uit te sluiten.

Als tinnitus inderdaad door hyperactiviteit in het centraal zenuwstelsel ontstaat, zouden anticonvulsiva een plausibele behandeling voor tinnitus kunnen vormen. In hoofdstuk 5 wordt een Cochrane review beschreven over zeven studies die vier verschillende anticonvulsiva onderzochten (gabapentine, carbamazepine, lamotrigine en flunarizine). Het merendeel van deze studies heeft een redelijk of hoog risico op bias omdat de gebruikte methodologie minimaal beschreven is. Vanuit deze studies is er geen bewijs voor een groot positief effect van deze anticonvulsiva op tinnitus, maar een klein effect (van twijfelachtige klinische waarde) werd wel aangetoond.

In hoofdstuk 6 wordt een dubbelblinde gerandomiseerd gecontroleerde studie over het effect op tinnitus van bilaterale repetitieve Transcraniële Magnetische Stimulatie (rTMS) van de auditieve cortex beschreven. rTMS met een lage stimulatiefrequentie kan inhibitie veroorzaken, wederom een plausibele therapie tegen hyperactiviteit in het centraal zenuwstelsel. Vijftig patiënten met chronische tinnitus die gezien waren door de Zorggroep Tinnitus werden in deze studie geïncludeerd. Bilaterale laagfrequente rTMS bleek niet effectief in de behandeling van tinnitus. Hoewel andere studies (patiëntenseries en cross-over studies) een positieve trend voor effect van rTMS lieten zien, zijn de gevonden effecten daarbij zo klein dat ze als klinisch irrelevant beschouwd zouden moeten worden. Er zijn tot op heden vier andere gerandomiseerd gecontroleerde studies verricht. Twee hiervan laten ook geen effect van rTMS zien, terwijl de andere twee studies wel een effect laten zien. Hoewel het hiermee lijkt alsof het afdoende is bewezen dat rTMS niet effectief is in de algehele tinnituspopulatie, blijft het betwistbaar of rTMS effectief is in bepaalde subgroepen van patiënten, met een andere stimulatiefrequentie of op een andere locatie van de hersenen dan de auditieve cortex. Gezien het gevonden effect in twee gerandomiseerd gecontroleerde studies die hun patiënten op de temporopariëtale overgang stimuleerden, is dit mogelijk een effectievere locatie voor rTMS dan de auditieve cortex. In de huidige studie werd een iets grotere verbetering gezien na rTMS bij patiënten met ernstigere tinnitus, maar dit effect was klinisch nog steeds klein.

Een probleem in tinnitusonderzoek is dat er geen universeel geaccepteerde uitkomstmaat voor tinnitus is. Verschillende tinnitusspecifieke vragenlijsten worden gebruikt om behandeleffecten te meten en een review over deze vragenlijsten is het onderwerp van hoofdstuk 7. In dit review worden zes verschillende gezondheidsgerelateerde kwaliteit van leven instrumenten geïdentificeerd die momenteel gebruikt worden om behandeluitkomsten in tinnitusstudies te meten: de Tinnitus Handicap Inventory, de Tinnitus Questionnaire, de Tinnitus Reaction Questionnaire, de Tinnitus Severity Index, de Tinnitus Handicap Questionnaire en de Tinnitus Severity Questionnaire. Geen van deze vragenlijsten bleek gevalideerd om de effectiviteit van therapeutische interventies te meten.

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1) C.E.L. Hoekstra, F.M. Wesdorp, G.A. van Zanten, Socio-demographic, medical and tinnitus related factors associated with tinnitus burden, revision submitted to *Ear and Hearing*

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About the author

Carlijn Emily Louise Hoekstra (1980) completed her secondary education in the year 1998 at the Praedinius Gymnasium Groningen. In the subsequent year, she studied at Beloit College, Wisconsin, USA, where she followed a pre-medical undergraduate program and was included on the Dean's list for her academic performance.

In 1999 she started the study Natural Sciences and Innovation Management at the University Utrecht for which she obtained her "propedeuse" degree. She started her medical study in 2000 at the University Utrecht, which she completed in 2006. She followed an extracurricular surgical internship in 2002 at Hasanuddin University Hospital in Makassar, Indonesia. In 2004 she performed a clinical study on the prevalence of HIV/AIDS and syphilis in Léon, Nicaragua, on which she published her first scientific article. Here, she also learned to speak Spanish. In 2002 she went on an expedition to become the first Dutch woman to ski the last degree to the North Pole.

Since 2006 the author has worked at the Otorhinolaryngology department of the University Medical Center Utrecht (UMC Utrecht). In the first two years she laid the foundation for this dissertation. She was one of the founders of the Tinnitus Care Group Utrecht, which she also coordinated in the following years. In 2008 she started her residency in Otorhinolaryngology and Head & Neck surgery at the UMC Utrecht. Rotations were done at the Gelderse Vallei hospital Ede with dr. Majoor, the Gelre hospital Apeldoorn with dr. van Benthem, and the Antonius hospital Nieuwegein with dr. Copper. In 2013 she became a board certified otorhinolaryngologist.

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