TINNITUS

A CBT BASED APPROACH

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Tinnitus, a CBT based approach.

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CHAPTER I

GENERAL INTRODUCTION

Introduction

The term 'Tinnitus Aurium', derived from the Latin words 'tinnire' (to ring) and 'aurium' (pertaining to the ears), refers to a continuous phantom auditory sensation in the absence of an external source. Tinnitus is in most cases perceivable only by the person reporting it, termed subjective tinnitus, though in certain cases it can be perceived by an external observer as well, in which case it is termed "objective" tinnitus. Most often the term tinnitus refers to "subjective" tinnitus, which is a very common sensation, and most commonly known as the 'ringing of the ears' often perceived indeed as a ringing, buzzing or hissing sound, though reports of hearing birds chattering, the sound of cruising jet-planes, or speech in undistinguishable voices do occur. Tinnitus is often experienced as a constant sound, though a pulsatile tinnitus, when rhythmic usually synchronous with the persons heartbeat, is fairly common as well. Tinnitus can be experienced as one single sound, or as a combination of different sounds, it can be localized in both ears, in one ear only, in the head, and even has been reported to originate around or outside the head. (Stouffer & Tyler, 1990; Tyler, 2000)

Tinnitus is an auditory phantom phenomenon often resulting in severe suffering, which has puzzled philosophers, physicians, and scientists alike throughout history. Mention of the symptom, now known as tinnitus, can be traced back as far as ancient Egyptian Ebers papyrus from the seventeenth dynasty B.C. (1650-1532), whereas the Greeks introduced treatment approaches as early as 400 B.C, first by Hippocrates and soon after by Aristotle, who advocated perceptually masking the tinnitus by external acoustic stimuli (Kraft, 1998). Moreover, throughout these past 3500 years the importance of the strong negative emotional connotation of tinnitus-like experiences seem to be commonly agreed upon (Dan, 2005; Dan & Pelc, 2005). The coinciding extreme anguish and suffering of some of the patients resulted in debate, questions, and therapeutic approaches as well. Interestingly, the primary and most advocated tinnitus treatment approach from ancient times up to this day has been the masking of the tinnitus sound by an external sound, hereby soothing the intrusiveness of the tinnitus. Additionally, it is also hard to find any treatment approach for tinnitus, whether audiological or psychological, without treatment elements aimed at decreasing the negative emotional reactions. Then, what has changed during these past 3000 or so years in our understanding, and treatment of this mysterious auditory experience? Is there truly anything new to report?

Epidemiology

Almost everybody experiences a transient tinnitus now and again, usually lasting 30 to 60 seconds, or has experienced a so-called ‘disco’-tinnitus, which can last up to a few days after prolonged exposure to loud sound. For 16 to 21% of the adult population tinnitus is a fairly common auditory sensation (Krog, Engdahl, & Tambs, 2010), and for a relatively small subgroup (3-6%) (Davis & Refaie, 2000), it becomes a chronic bothersome and incapacitating symptom, seriously interfering with all aspects of daily life (Cima, Vlaeyen, Maes, Joore, & Anteunis, 2011). Data on the prevalence of tinnitus vary widely as a result of ambiguity in defining tinnitus. The most recent study on the prevalence of tinnitus in a large general population sample (n=51.574) reported that 16 – 21% of the sample responded ‘yes’ to the question: ‘Are you bothered by a ringing in your ears?’ (Krog, et al., 2010). For 7 – 12% of this sample tinnitus was frequently bothersome, and 2– 4% was almost always bothered by it.

Sudden onset of tinnitus is common, though a large portion of patients report a gradual increase of the tinnitus perception. Prevalence of tinnitus among men and women is comparable, and increases with age (Gopinath, McMahon, Rochtchina, Karpa, & Mitchell, 2010a). Reports on the prevalence of tinnitus in childhood are scarce, though it seems that prevalence amongst children is comparable to the prevalence in the adult population (Baguley, Bartnik, Kleinjung, Savastano, & Hough, 2013).

Reports on the incidence of tinnitus are scarce. In one study a large cohort of individuals aged 43-84 years, not reporting tinnitus at baseline, was followed. In this study a person was identified as having tinnitus when the tinnitus was at least moderately severe or interfered with sleep (Nondahl, et al., 2010; Nondahl, et al., 2002). The 5-year incidence of new cases of tinnitus was 5.7, and the 10 year incidence was 12.7.

A high risk factor of developing tinnitus is hearing loss (Gopinath, McMahon, Rochtchina, Karpa, & Mitchell, 2010b), however a large proportion of patients show audiometrically normal hearing. Other risk factors associated with tinnitus are psychological trauma, occupational and recreational noise exposure, and cardiovascular disease and hypertension as well. Tinnitus is a common co-morbid symptom in several otological disorders such as Meniere's disease (a disorder of the inner ear leading to vertigo and balance problems) and Otosclerosis (an abnormal growth of the inner ear bones). Hyperacusis (a hypersensitivity to sound) is reported in approximately 40% of people with tinnitus complaints and 86% of people who mainly complain of increased sensitivity to sound, report a coinciding tinnitus (Davis & Refaie, 2000).

Causes

The causes of tinnitus are still largely unknown; a well accepted theory on the aetiology of tinnitus is the hypothesis that tinnitus occurs as a result of spontaneous anomalous neural activity at any level along the auditory axis (Ahmad & Seidman, 2004). In other words, in case one perceives a tinnitus, it is probable that somewhere along the path from the cochlea to the brain, changes occur, which lead to altered brain patterns, perceivable by the individual as a sound. These changes have been hypothesized to occur on individual cell-level, on the level of regions of cells as well as on the level of broader cortical networks (De Ridder, Elgoyhen, Romo, & Langguth, 2011). Since the most common diagnoses coinciding with tinnitus involve disorders of the cochlea, these have been hypothesized to be the main cause of neuronal anomalies (De Ridder, et al., 2004; De Ridder & Van de Heyning, 2007). The exact cause is as of yet still to be discovered.

Theories about the cause of tinnitus

Theories regarding the nature and cause of tinnitus are evolving, and different pathofysiological neurological mechanisms have been hypothesized. Since high frequency hearing loss is one of the major predictors of developing tinnitus, this loss of sensory input has been hypothesized to result in neurological responses, such as the generation of auditory stimuli by the nervous system itself (Eggermont & Roberts, 2012). More likely, not the peripheral changes, but the changes along the more central auditory neural pathways are considered to cause the tinnitus percept (Eggermont, 2012). It has been hypothesized that on the individual cell-level the tinnitus is generated as a result of increased spontaneous firing rated of neurons, due to a change in the down-regulation of cortical inhibition on these cells. Alternatively, neuronal synchronicity, in which neurons in the deprived region tune into the properties of the adjacent neurons, has been proposed as the mechanism causing tinnitus (Norena & Farley, 2012). Last, in parallel with findings in chronic and phantom pain research, chronic bothersome tinnitus has been associated with the involvement of broader cortical networks, other than auditory, such as prefrontal regions and the limbic system (De Ridder, et al., 2011). The involvement of the limbic system and in particular the autonomic (sympathetic) nervous system is considered to be the main reason for clinically relevant subjective tinnitus. This is further supported by the observation that psychological components accompany the tinnitus sensation, and that these have shown to be significant predictors of tinnitus suffering (Ahmad & Seidman, 2004). The involvement of the above mentioned brain structures is corroborated by the finding that tinnitus induces distress in only a small part of the individuals perceiving it and that in this case the acoustical characteristics of the tinnitus (e.g. loudness) is not correlated to the severity of the tinnitus or to treatment outcome (Jastreboff, 1990). In addition, onset of tinnitus often occurs long after the onset of the original hearing disorder, frequently coinciding with stressful life events. Stress can either induce or aggravate the tinnitus (Coles & Hallam, 1987). Involvement of the limbic system and the autonomic nervous system indicate that physiological, emotional, cognitive, and behavioural aspects are important in the maintenance of chronic tinnitus complaints. Specifically, the involvement of the limbic system (Jastreboff, Gray, & Gold, 1996) suggests that fear and fearful reactions related to the tinnitus have been hypothesized to be pivotal, which has been corroborated by recent findings as well (Cima, Crombez, & Vlaeyen, 2011; Kleinstauber, et al., 2012).

Assessment

Assessment of tinnitus severity has been frequently debated in the past (McCombe, et al., 2001). When the tinnitus has a rhythmical or pulsatile nature, it is usually advised to first investigate with auscultation whether it is an 'objective' tinnitus, and whether treatment of an underlying identifiable pathology is indicated. However, since tinnitus in the large majority of patients is of the subjective type, the experience of the auditory sensation is non-observable, and objective quantification is difficult. The more objective measurements of tinnitus (such as tinnitus pitch and loudness measurements) have not been successful as diagnostic tools, nor has a useful relationship been established between perceived psycho-acoustic characteristics, and severity of complaints (Andersson, 2003; Henry & Meikle, 2000; Westin, Hayes, & Andersson, 2008). Consensus seems to exist that the psychological reactions to the unwanted stimulus are the most important element in defining the severity of complaints as opposed to the signal (sound) itself. Severe emotional distress (high levels of depression and anxiety), major declines in concentration, sleeping difficulties and problems in directing attention are some of the impairments caused by tinnitus (Andersson, Lyttkens, & Larsen, 1999; Erlandsson & Hallberg, 2000; Jastreboff, 1990). The need for identification and the classification of tinnitus suffering, as well as the need to compare effects of interventions led to the development of many different outcome measures (Kamalski, Hoekstra, van Zanten, Grolman, & Rovers, 2010). Early measures included use of daily dairies that may have served to add to the unreliable measures of tinnitus loudness and pitch assessments (Ireland, Wilson, Tonkin, & Platt-Hepworth, 1985). Later, tinnitus-specific health-related measures, like the Tinnitus Questionnaire (Hallam, Jakes, & Hinchcliffe, 1988) and the Tinnitus Handicap Inventory (Newman, Jacobson, & Spitzer, 1996; Newman, Sandridge, & Jacobson, 1998), were developed in order to assess distress due to tinnitus, or impact of the tinnitus on the individual. Other similar measures include the Tinnitus Reaction Questionnaire (Wilson, Henry, Bowen, & Haralambous, 1991), the Tinnitus Handicap Questionnaire (Kuk, Tyler, Russell, & Jordan, 1990), the Tinnitus Severity Index (Meikle, Griest, Stewart, & Press, 1995), and the most recently proposed The Tinnitus Functional index (Meikle, et al., 2012). All of these measures are developed to assess various factors hypothesized to be of importance in the overall suffering of tinnitus. All of them assess in some form emotional and cognitive impairments, psychological distress, and daily life difficulties such as hearing problems, concentration ability, and sleep disturbance as a result of the tinnitus. These measures were developed mainly for the clinical assessment of tinnitus, and less for the comparison of treatment outcomes. Most clinical guidelines suggest to include the following assessments to classify patients and indicate treatment; 1] audiometry to assess hearing loss, 2] a pitch and loudness match assessment to define the sound-characteristics of the tinnitus, and 3] one of the measures described above, to assess psychological distress as a result of the tinnitus (Cima, et al., 2009; Hoare, Gander, Collins, Smith, & Hall, 2012; Tyler, Haskell, Gogel, & Gehringer, 2008).

Treatment

As tinnitus is not a disease, but merely a symptom, a cure through medical or pharmacological interventions has not been found (Elgoyhen & Langguth, 2010; Elgoyhen, Langguth, Vanneste, & De Ridder, 2012). The most widely implemented treatment strategy is aimed at the sound perception level, by use of external sound, either by specifically designed ear-level devices (tinnitus maskers), or by prescribing hearing aids to amplify the surrounding sound. The use of sound therapy for tinnitus, use of ear-level SGs, or the avocation of sound enrichment, has become a mainstream tinnitus intervention since the theoretical publications by Jastreboff (Jastreboff, 1990; Jastreboff & Hazell, 1993). However, evidence for the effectiveness of these approaches have a not been established (Hoare, Kowalkowski, Kang, & Hall, 2011; Hobson, Chisholm, & El Refaie, 2010; Phillips & McFerran, 2010). Moreover, neurophysiological change by sound enrichment or masking and evidence on changes in tinnitus perception or disability by the use of these techniques, have been judged to be of insufficient quality and not robust enough to guide current tinnitus treatment (Hoare, Stacey, & Hall, 2010). Accumulating evidence indicates that chronic tinnitus suffering can be alleviated by using a psychological treatment approach (Henry, Dennis, & Schechter, 2005; Henry, Schechter, et al., 2005). In particular, cognitive- behavioural approaches have repeatedly been shown to significantly reduce distress as a result of the tinnitus, reduce anxiety, and depression, and improve quality of life and daily functioning for patients with bothersome tinnitus (Andersson, 2002; Andersson & Lyttkens, 1999; Hesser, Weise, Westin, & Andersson, 2011; Hoare, et al., 2011; Martinez-Devesa, Perera, Theodoulou, & Waddell, 2010). Moreover, for many years now almost every proposed intervention for tinnitus, whether audiological or psychological, includes management of negative reactions to the sound and has included some form of education, counseling, or psychological treatment as one of its key elements. Mono-disciplinary treatment protocols are rare in the literature since even the approaches directed toward the sound-perception level include some form of counseling for patients (Henry, et al., 2007; Henry, Schechter, et al., 2005; Henry & Wilson, 1996; Henry, Zaugg, Myers, Kendall, & Turbin, 2009; Jastreboff, 2007; Tyler, et al., 2008; Wilson, Henry, Andersson, Hallam, & Lindberg, 1998). Researchers and clinicians alike seem to agree that a major part of tinnitus suffering can be understood by examining the negative psychological reactions caused by it, and that these reactions need to be addressed properly in order to effectively manage complaints (Jacobson, 2012; Langguth, Kleinjung, & Landgrebe, 2011; Meikle, et al., 2012).

Standard Care

As has been summarized above, tinnitus treatment approaches, outcome assessments, and study protocols vary widely, leading to many forms of tinnitus treatments, many diagnostic tools, and study outcomes that are often difficult to compare (Cima, et al., 2009; Hoare, et al., 2012). Moreover, the state of current evidence is based on studies of low methodological quality, and a standard treatment approach, a standard diagnostic heuristic, or consensus about comparable outcomes are lacking(Landgrebe, et al., 2012).

Aim and outline of the present thesis

The aim of the current thesis is to test new cognitive behavioural concepts in tinnitus research, assessment and treatment approaches. These concepts might present new avenues for treatment, assessment and research within the tinnitus field, as well as directions for the refinement of current usual care, leading to an effective more standardized approach in tinnitus health care in general.

Chapter 2 presents a review of multi-disciplinary tinnitus treatments. The aim is to systematically summarise and evaluate previous literature on tinnitus treatment approaches that incorporate various elements from audiology and psychology. Based on the evidence a treatment strategy for chronic subjective tinnitus is suggested, and a treatment protocol is proposed.

In Chapter 3, a novel measure for tinnitus related interference in daily life functioning is introduced. Although tinnitus questionnaires with excellent psychometric properties already exist, they are often conceptually hybrid, in that they measure a variety of different constructs. Even though these can be of high value in clinical practice and research outcome studies, difficulties arise when a researcher wishes to investigate underlying the mechanisms in tinnitus suffering, or compare tinnitus to other chronic health problems. The need for a more focused measure of interference in daily life functioning arose, and the Pain Disability Index (Tait, Chibnall, & Krause, 1990) was modified into the Tinnitus Disability Index (TDI), and subsequently evaluated on its psychometric qualities.

In Chapter 4, a number of relevant psychological concepts are introduced, which are expected to mediate or moderate the impact of tinnitus on daily functioning. First, since part of tinnitus-related distress seems to be associated with misinterpreting the sound, and in order to establish tinnitus-related cognitive attributions, the concept of tinnitus catastrophising will be introduced, as well as a measure to assess this concept. Second, next to symptoms of anxiety as have been proposed previously, we propose that tinnitus-related fear has a specific and key role in the development of tinnitus suffering. Third, tinnitus-related increased awareness is introduced as a possible predictor for increased tinnitus-related distress.

In Chapter 5, a clinical research protocol is presented. A standard approach in tinnitus health care, a common diagnostic heuristic, or effective treatment strategy is lacking. Cognitive behavioural therapy (CBT) has received most empirical evidence in relieving tinnitus complaints. Best-practice evidence indicates that audiological treatment elements are mostly based on standard TRT protocol, since this approach offers guidelines in audiological counseling and educational purposes. Therefore, a large scale randomized controlled trial is proposed, to study the effectiveness and cost-effectiveness of a CBT-based tinnitus treatment protocol, including the counseling elements from TRTs, as compared to care as usual. Care as usual is modelled after the standard care as is provided by a typical audiological centre in the Netherlands. A stepped wise organization of the treatment arms is proposed, in which the intensity of health care increases in steps, serving the largest part of the patient population with a fairly short treatment, which allows allocation of additional resources for those suffering on a more severe level in a second step.

In Chapter 6, the results of the RCT are discussed. First, treatment fidelity is assessed by a protocol-adherence and contamination check. Second, treatment outcomes are evaluated by multilevel mixed regression employing intention-to-treat analyses; final analysis includes all participants for whom baseline data on primary and secondary outcomes is available. Third, post hoc moderation analyses are performed to check whether differences in effects between CBT-based tinnitus treatment and care as usual is dependent upon the level of tinnitus severity as measured at baseline.

Chapter 7 presents an extensive economic evaluation, based on the RCT outcome evaluations, comparing care as usual with the specialised CBT based treatment, with the primary effect parameter being the Quality Adjusted Life Year (QALY). Costs include tinnitus related health care costs; both for care consumed at the treatment centre as well as care provided in other medical settings, patient and family costs, and costs for loss of productivity. Cost-effectiveness analyses are performed from both the societal and the health care perspective and an incremental cost effectiveness ratio (ICER) is calculated.

In Chapter 8, the mediating role of tinnitus-related fear in the reduction of tinnitus complaints as a result of CBT with TRT elements is examined. As was introduced in chapter 2, tinnitus-related fear was expected to predict the onset and maintenance of chronic tinnitus related suffering. In order to investigate the mediating role of tinnitus related fear on treatment effects, post hoc analyses on the outcomes of the RCT were performed and discussed.

Finally Chapter 9 provides a general discussion of the main findings. The two main theoretical models are presented and compared. The main results of the studies are summarized and an integrated discussion of findings and their implications are provided. Last, limitations and directions for future research are considered.

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CHAPTER II

MULTIDISCIPLINARY TINNITUS TREATMENT; A SYSTEMATIC REVIEW

Submitted as

Cima, R.F.F., Scheijen, D.J.W.S., Joore, M.A., Anteunis, L.J.C., & Vlaeyen, J.W.S. (2013). Multidisciplinary tinnitus management; audiological and psychological treatment approaches, a Systematic Review.

Abstract

Tinnitus can be defined as an auditory perception, without the presence of an external source. The purpose of the current review is to systematically investigate previous literature on tinnitus-treatment approaches incorporating different elements from audiology and psychology. Follow up, case control, clinical trials, randomized controlled trials, and reviews assessing multi-element treatment approaches were identified as a result of an electronic database search. A total of 21 (of the initial 216 studies) were included in this systematic review of literature. The results suggest that current treatment approaches in tinnitus management are highly diverse; consisting of a combination of different tinnitus diagnostics, treatment elements and outcome assessments. Furthermore, tinnitus treatments seem hardly comparable; intervention studies are low in methodological quality, exhibiting low level of evidence. A multidisciplinary treatment approach was investigated in almost all studies, combining different treatment elements, in which health care is organized in accumulating steps. The optimal treatment strategy might be best CBT-based, organized multi-disciplinary, using a stepped-care approach, by which the majority of tinnitus patients can be treated effectively with a fairly short intervention, and additional treatment steps can be indicated for those suffering on a more severe level.

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Introduction

Chronic tinnitus suffering can be described as the continuous perception of a noxious internal sound, not generated in the external environment. Up to 6% of the general adult population is severely impaired by tinnitus, experiencing problems in almost all aspects of their daily functioning. (Cima, Vlaeyen, Maes, Joore, & Anteunis, 2011; Davis & Refaie, 2000) It has been suggested that it is not the tinnitus sound causing the suffering, since the largest group (approximately 21%) (Krog, Engdahl, & Tambs, 2010) is not particularly bothered by it. For the smaller part of this group however, the percept of this bothersome interfering sound has been associated with severe sleep deprivation, cognitive malfunctioning, anxious and depressive moods and impaired social functioning.(Davis & Refaie, 2000; Goebel, Keeser, Fichter, & Rief, 1991; Hiller, Goebel, & Rief, 1994; Lindberg, Scott, Melin, & Lyttkens, 1988a) Tinnitus is not only an audiological problem. Chronic bothersome tinnitus seems a condition with severe emotional and cognitive consequences, leading to tinnitus-related psychological distress. Interestingly, these negative psychological reactions as a result of the tinnitus significantly predict severe suffering whereas the audiometric characteristic (like loudness or pitch) of the tinnitus sound hardly do. (Andersson, 2003; Henry & Wilson, 1995; Hiller & Goebel, 2007)

Since the tinnitus perception is not easily measured or quantified objectively, and medical curative efforts have been unsuccessful so far, effective management of tinnitus complaints has been a difficult assignment requiring a multitude of disciplines and usually prolonged fragmented trajectories (Cima, et al., 2012; Greimel, Leibetseder, Unterrainer, & Albegger, 1999; Henry & Meikle, 2000; Hoare, Gander, Collins, Smith, & Hall, 2012). As the psychological correlates (i.e. emotional, cognitive and attentional) of tinnitus influence tinnitus suffering, cognitive behavioural therapy (CBT) treatment elements have been increasingly incorporated in tinnitus management (Andersson & Lyttkens, 1999a; Dobie, 1999; Hesser, Weise, Westin, & Andersson, 2011; Martinez Devesa, Waddell, Perera, & Theodoulou, 2007). Next to these CBT approaches, therapies aimed at the acoustic characteristics of the tinnitus at the sound perception level, such as tinnitus masking therapy (TM) or tinnitus retraining therapy (TRT), are offered widely as well. These sound-based approaches aim to ameliorate tinnitus distress by means of education, counseling, and exposure to a neutral external sound, by use of a sound generating device, based on a specific protocol (Henry, Zaugg, &

Schechter, 2005a, 2005b; Jastreboff, 1999; Jastreboff & Hazell, 1993; Schechter & Henry, 2002). Throughout the literature on effective tinnitus management, it is hard to find either CBT or sound-based approaches as the sole treatment. In the effort to effectively manage complex tinnitus problems, treatment packages usually consist of a mixture of treatment approaches. Combinations of counseling, sound therapy and additional CBT approaches have been proposed to effectively reduce the impact of the tinnitus on functioning (Henry & Wilson, 1996; Schechter & Henry, 2002; Tyler, Haskell, Gogel, & Gehringer, 2008). However, none of these have led to the implementation of a specific treatment strategy on a large scale, since research of sufficient methodological quality, generating comparable outcomes, has been scarce (Cima, et al., 2009; Hoare, et al., 2012; Tyler, et al., 2008). This leaves patients and professionals alike with a myriad of options and combinations of treatment approaches. Next to the highly diversified treatment approaches, many different outcome measures and clinical assessment batteries can be found, whether it concerns audiometry, severity, intensity, acoustic properties, daily life impact, or psychological distress associated with tinnitus, leading to difficulties reaching consensus and as a result, comparable research outcomes (Hoare, Kowalkowski, Kang, & Hall, 2011). In a recent evaluation of current practice in tinnitus management in the United Kingdom (Hoare, et al., 2012), this lack of standardized practice and consensus in tinnitus services was clearly illustrated. Hoare et al (2012) concluded that we are faced with difficulties in; discerning key factors for best practice, establishing good quality of care, and equal access to effective care for patients, additionally we are faced with limited translational research outcomes.

Apart from the difficulties in tinnitus treatment and research as highlighted above, there seems to be some consensus about proper tinnitus management, in that more often than not it incorporates a combination of treatment elements, carried out by a multidisciplinary team. Currently we aim to provide a review of past research on tinnitus management using this multidisciplinary or combination approach, i.e. incorporating sound-based approaches (including audiological diagnostics and counseling), counseling/education, and CBT treatment elements (including group treatment and psychosocial counseling). Secondly, an overview of the outcome assessments will be provided. Finally, based on these results, we aim to propose an assessment and treatment strategy for standard-care tinnitus management.

Search method for the identification of studies

In the literature on tinnitus treatment, discrepancy in terms and treatment classification, as well as a high diversity in treatment outcome measures occurs often. Furthermore, most tinnitus treatments in audiology are multidisciplinary by nature and usually consist of several therapeutic approaches and counseling, including sound-based therapy, tinnitus retraining therapy, cognitive behavioural coping techniques, relaxation therapy, stress management, biofeedback and more extensive audiological counseling. Therefore we used a rather broad range of search terms to ensure inclusion of all relevant studies performed on tinnitus management approaches and a wide range of outcome measures. All systematic reviews, reviews, and Meta analyses were included as well. The last search was carried out in November 2011.

Search terms

Tinnitus AND trial AND review (OR management OR care, OR specialised clinic, OR multidisciplinary, OR therapy, OR treatment, OR systematic, OR meta analysis, OR cognitive behavioural, OR psychological, OR relaxation OR education OR quality of life, OR stress, OR distress, OR coping, OR anxiety, OR depression, OR chronic, OR pain, OR costs, OR cost analysis, OR effects, OR outcome assessment OR sound therapy OR TRT) NOT (Complementary Therapies, OR Acupuncture, OR Ginko biloba, OR surgery, OR pharmacology, OR Internet).

It is important to note that he second search term 'Trial' includes studies using other methodological designs than randomised controlled trial (RCT) only, this according to the MeSH thesaurus.

Population: Adult tinnitus population

Intervention: Multidisciplinary care, specialised clinic, cognitive behavioural therapy, psychological treatment, relaxation, education, tinnitus retraining, TRT (sound therapy), sound therapy, counseling

Outcome Measures

Quality of life, stress/distress, depression, anxiety, coping, tinnitus distress / handicap/ impairment / severity

Methodological filters

Systematic review, RCT, follow-up of cohort design, case control study

Electronic Databases

Medline (1980 – present), Psychinfo (1972-present), Psyarticles, Cinahl (1982 – present), ERIC database (1966 – present), Econlit, DARE database, Education Resources Information Centre, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Controlled Trials Register, Cochrane Methodology Register, NHS Economic Evaluation Database, Health Technology Assessment Database, Cochrane Database of Methodology Reviews (CDMR)

Number of manuscripts retrieved

After performing the first search strategy described above a total number of 216 manuscripts were retrieved (Medline: 125; Psychinfo: 20; Psyarticles: 3; Cinahl: 14; ERIC: 11; Econlit: 2; DARE: 36; Cochrane: 5).

Selection procedure

Assessment of the abstracts of the retrieved manuscripts resulted in 27 relevant studies. The following studies were included:

Systematic reviews, meta analyses, reviews, RCT's and other trials comparing different treatment combinations, including sound therapy, counseling, behavioural modification, relaxation, attention diversion and exposure, biofeedback, coping strategies, specific tinnitus management programmes, and multidisciplinary approaches.

Not included were studies on mono-disciplinary pharmacological treatment, complementary or alternative treatments, and studies on animal-models and neuro-magnetic stimulation. Treatments exclusively provided through the internet, were excluded as well, since these were considered complementary and not a main treatment approach.

Validity assessment

Two reviewers (RFFC and DJWS) independently assessed abstracts of all selected studies on inclusion quality, using above described criteria. Disagreement was resolved by consensus, having both reviewers reading the full eligible study.

Results

The total number of selected manuscripts was 21, of which 3 follow-up or case control studies, 2 controlled not randomized trial, 8 randomized controlled trials, and 8 review studies (including scoping, systematic, and meta-analytical reviews). Since it was found that the reviews we included have some overlap with the present one, they will be summarized in light of the present findings in the conclusion. In the Appendix a summary of the characteristics of all included studies is provided, table 1 provides an overview of the different treatment elements per study, and below a summary of each study separately is given. For each study, drawbacks and limitations were assessed and are summarized as well. Information about each study is provided in order of study design and in chronological order, in the appendix, tables, as well as in the summary. We make a distinction between case-control studies, non-randomized clinical outcome studies, RCT's, and reviews.

TABLE 1. INVESTIGATED TREATMENT ELEMENTS IN THE COMPARATIVE STUDIES (REVIEWS NOT INCLUDED)

Study/Treatment elements	a	b	c	d	e	f	g	h	i	j
Lindberg et al, 1988	x	x		x				x		
Lindberg et al, 1989	x	x				x	x	x	x	
Davies et al, 1995			x	x	x			x		
Kröner-Herwig et al, 1995		x		x	x		x	x	x	
Andersson, 1997		x	x					x		x
Wise et al, 1998				x	x				x	
Kröner-Herwig et al, 2003		x		x	x	x		x	x	
El Refaie et al, 2004	x	x	x	x	x			x	x	
Zachriat & Kröner-Herwig,2004	x	x	x	x	x				x	
Herraiz et al, 2005	x	x	x							
Hiller & Haerkötter, 2005	x	x	x	x	x	x		x		
Henry et al, 2006	x	x	x			x				
Henry et al, 2007	x	x				x				

a. Audiological/medical diagnostics/ rehabilitation
b. counseling/education
c. Masking/Sound therapy/sound generating device
d. Cognitive techniques /control techniques
e. Attention diversion redirecting training
f. Exposure to external sound/ to avoid tinnitus
g. Breathing, bodily awareness, yoga
h. Relaxation therapy; progressive/passive/applied
i. Problem solving/ analysis/general life help/ stress- behavioral analysis
j. Other, acupuncture, medication

Assessment of risk of bias of included studies

The criteria of assessment were based on the Cochrane recommendations (Higgins & Green, 2008), and the following classification was used for determining the quality of the included studies; *Selection bias*: adequate randomization, allocation concealment, adequate definition/description of the included sample; *Performance bias*: blinding of participants and personnel; *Detection bias*: validity of assessment (blinding of outcome assessment/standardized measures); *Attrition bias*: complete outcome data (dropout /exclusions); *Reporting bias*: non-selective outcome reporting . In table 2 a summary of the risk of bias assessment is provided for each included study.

TABLE 2. ASSESSMENT OF RISK OF BIAS

Study/bias	a	b	c	d	e
Lindberg et al, 1988	-	-	-	?	-
Andersson, 1997	-	-	-	?	-
El Refaie et al, 2004	-	-	-	+	+
Herraiz et al, 2005	-	-	-	?	+
Henry et al 2006	-	-	-	?	-
Lindberg et al, 1989	-	-	-	?	-
Davies et al, 1995	-	-	-	+	-
Kröner-Herwig et al, 1995	-	-	-	+	-
Wise et al, 1998	-	-	-	-	-
Kröner-Herwig et al, 2003	-	-	-	-	-
Zachriat & Kroner-Herwig, 2004	-	-	-	-	-
Hiller, & Haerkötter, 2005	-	-	+	?	-
Henry et al, 2007	+	-	+	?	+

a. Selection bias: adequate randomization, allocation concealment, adequate definition/description of the included sample
b. Performance bias: blinding of participants and personnel
c. Detection bias: validity of assessment (blinding of outcome assessment/standardized measures)
d. Attrition bias: complete outcome data (dropout /exclusions)
e. Reporting bias: non-selective outcome reporting

Summary

FOLLOW UP OR CASE CONTROL STUDIES

In a follow-up study (Lindberg, Scott, Melin, & Lyttkens, 1988b) an individual behavioural therapy was evaluated, including next to CBT, first audiological diagnostics and counseling, tinnitus counseling and education, and within the behavioural therapy various relaxation techniques and tinnitus control procedures. Included were 75 moderate to severe tinnitus sufferers. Outcome measures were 1-week daily self-recordings (on 4 time points) of *tinnitus-discomfort* and *general mood*, tinnitus matching, i.e. *loudness and pitch* (2 time points), and a tinnitus-interview (unspecified) was taken at 2 time points. Significant overall reductions of *discomfort from tinnitus* and improvements in *general mood* were found at the 3 month follow-up, as measured by the self-recordings. At the three-month follow-up interview, 74% of the patients reported *improvements in tinnitus complaints*; however acoustic characteristics of the tinnitus, i.e. *loudness or pitch* did not change as a result of the behavioural treatment. Most noteworthy drawbacks in this study are that not all outcome assessments were reported and the treatment was not standardized and differed per patient.

Andersson (Andersson, 1997) evaluated differences between tinnitus patients who have received prior psychological treatments and untreated patients. Tinnitus patients (n=69) seeking treatment were asked about prior treatments, and were included when the most salient prior treatment was a psychological treatment. They completed a shortened version of TQ to measure *tinnitus complaints.* Four groups were obtained: No treatment (n = 24), acupuncture (n = 19), relaxation (n = 13), and other treatments (n = 13). Results showed minor differences between the groups using the TQ, the exception being that the previously untreated group showed more acceptability for change. It was suggested that most patients may have tried at least one treatment when entering a new treatment clinic; therefore it was stressed that the spread of nonspecific and non-effective treatments in the management of tinnitus should be avoided. Limitations of this study include the lack of pre-treatment data, and incomplete data on prior treatments other than psychological.

El Refaie et al. followed 57 tinnitus patients attending a specialised tinnitus clinic during one year (El Refaie, et al., 2004). Measurements on *tinnitus characteristics* and *severity, general quality of life*, and *quality of family life* were taken pre- and post attendance. A stepped care approach was employed, whereby for the whole group medical, audiological diagnostics and intervention was provided, tinnitus was assessed by matching procedures, followed by audiological counseling and education. Two-thirds of the patients then proceeded to a second step, including follow-up medical procedures, and individual therapy with a psychologist for CBT (unspecified), general counseling and problem solving, relaxation training, masking-/ hearing instrument fittings and follow ups with an audiologist. Results indicated a significant reduction in tinnitus annoyance, functional handicap and social handicap, as well as a significant improvement in general quality of life. Quality of family life showed improvement though no statistical significance was reached. Limitations of this study include the lack of data on effectiveness of step 1 only vs. additional step 2 care, no data about the number of patients receiving step 2, the period between assessments was undefined, and treatment (clinic attendance) included a broad range of treatment elements.

CLINICAL TRIALS NON-RANDOMIZED

Herraiz et al performed a long-term follow up clinical trial (Herraiz, Hernandez, Plaza, & Santos, 2005) in which 158 participants were divided in 4 groups: a tinnitus retraining therapy (TRT) group with the use of sound generators (N=68), and one without (N=48), a waiting list control group (N=21), and a partially treated group (N=21), including patients who refused to try sound generators. Patients were followed during 12 months, with baseline, 6 month, and 1 year measurements on *subjective improvement* (feel better, same, or worse), *tinnitus intensity and annoyance* (VAS), and *tinnitus disability* (THI). In the TRT group both with and without sound generators, 82% reported to feel better, and had improved tinnitus disability, both of which differed significantly compared to WLC and PTG. Tinnitus intensity and annoyance improved in the TRT group both with and without sound generators, when compared to WLC, but not when compared to PTG. No additional treatment affect was found for use of sound generators. It is important to note that resistance to TRT was defined when subjects experienced psychological distress or emotional problems. They state that simultaneous treatment of psychological problems, when present, is mandatory for TRT to be effective. Other drawbacks include the quasi randomization and the fact that there were significant baseline differences between the groups on baseline measurements.

Another non-randomized trial (Henry, et al., 2006a) included 123 severe tinnitus suffering veterans who were alternately allocated to either a tinnitus masking group (TM), or a tinnitus retraining group (TRT) group. The TM group was prescribed sound generators to be worn as was ‘comfortable’ for patients, up until the point the tinnitus was completely masked, in combination with unspecified counseling. The TRT group was treated according to protocol (Jastreboff & Hazell, 2004) in which the masking sound is adjusted just below the point where the loudness of the tinnitus and noise begin to mix, combined with standard TRT counseling by use of the Neurophysiological model(Jastreboff & Hazell, 1993). *Tinnitus disability* and *tinnitus severity* were assessed at baseline and at 3, 6, 12, and 18 months into the trial. Results indicated that TM is more effective after 3 months and TRT has more positive results on the longer term, i.e. 6, 12, and 18 months on all outcome measures, especially for patients with more severe tinnitus at baseline. Both approaches seemed effective though. Drawbacks in this study include the quasi randomization, the study sample which included predominantly veteran males suffering severely from tinnitus, a long period of treatment time participants had to commit to (18 months), no follow up data, the TRT group received more hours of counseling in a more structured manner, and TM and TRT were each carried out by a specialist in the respective fields, which was not controlled for in the trial.

RANDOMIZED CONTROLLED TRIALS (RCT)

Lindberg et al. (Lindberg, Scott, Melin, & Lyttkens, 1989) randomly assigned 27 patients to either a behavioural control treatment (relaxation and exposure to external pre-recorded daily life sounds, RE-group), a cognitive control treatment (relaxation and control techniques by distraction using the relaxation techniques and mental images, the RD-group), or a waiting-list control group (WLC). Primary outcomes were *tinnitus-loudness, tinnitus-discomfort and tinnitus-controllability*, as measured with visual analogue scales (VAS) (before, while, and after exposure to a 1 minute pre-recorded sound, measured daily during a 1 week period), tinnitus matching on *tinnitus loudness and pitch*, and finally a questionnaire (unspecified), but only at follow-up. Measurements were taken pre-, during- and two week after treatment for the VAS self- recordings of loudness, discomfort and controllability, pre- and post treatment for the tinnitus matching procedure, and the questionnaire was sent to patients after treatment ended. The main finding was that behavioural treatment (where RE and RD where analysed as 1 group) reduced subjective loudness and discomfort from tinnitus, and increased the patients' ability to control these distressing experiences, as compared to the WLC. No group differences were found between the RE and RD group on any of the outcomes or time points, and no differences were found in acoustic properties of the tinnitus, i.e. loudness or pitch ratings. Noteworthy limitations are; the lack of reporting differences between RE and RD, treatments were similar in both groups, the non-standardized loudness measurements, and missing measurements on two of the outcomes.

In another randomized controlled trial, three forms of CBT were compared (Davies, McKenna, & Hallam, 1995). Patients (n=30) were randomly assigned to either passive relaxation PR, applied relaxation AR, or individual cognitive therapy ICT. A 4 repeated measures design (pre-, and post-treatment, and 1 and 4 month follow-ups) was carried out. *Loudness and annoyance* of the tinnitus was measured on a subjective rating scale on all time points. T*innitus effects* (psychological distress, auditory perception, and sleep difficulties) were measured with the Tinnitus Questionnaire (TQ), (Hallam, Jakes, & Hinchcliffe, 1988) on all time points. G*eneral depression* and *anxiety* were only measured at pre-treatment and at 1 month follow-up. D*aily rating of loudness, annoyance, and insomnia* were only measured during treatment. In addition the principle investigator conducted an interview with participants at 4 month follow-up to assign to either 'no remaining problems' or 'slight remaining problems' or 'significant remaining problems'. Results from this RCT indicate no significant effects of either of the treatments, on any of the measures from pre treatment to 4 month follow up. Important to note is that; investigators removed data from 1 treatment group from the analyses, data on outcomes on some of the time points were unavailable, and that considerable between-group differences at baseline were found, making results from this study difficult to interpret.

Kröner-Herwig compared cognitive-behavioural group therapy with yoga group training, and a waiting list control group (Kröner-Herwig, et al., 1995). Patients (n=43) were randomly assigned to either CBT (N=15) which included education, coping techniques, attention training and progressive relaxation, or to a Hatha-yoga group (N=9), which included relaxation, bodily awareness training and breathing exercises, or a self-monitoring control condition (N=19). All treatment groups received 10 two-hour sessions. Participants were assessed at baseline, directly after treatment, and at 3 months follow-up.

Measurements included *audiometry* (only at baseline), tinnitus matching procedures, i.e. *loudness and pitch*, assessment of *tinnitus severity* by the TQ, a *self-monitoring diary* period of 3 weeks (assessment of tinnitus loudness, discomfort, sleep disturbance, interference with activity, control of tinnitus, and hours per day that tinnitus could be ignored), assessment of *general wellbeing*, and *depression*. Results showed that CBT showed significant increases in self-efficacy and control over tinnitus and a decrease in worry about and disturbance from tinnitus as compared to the yoga treatment, and the waiting list group. Furthermore, CBT patients were generally more satisfied with the treatment than the yoga-treated participants. The acoustical characteristics of the tinnitus, i.e. loudness and pitch, did not change over time in any of the groups. Limitations of this study are; lack of psychometric quality of the main outcome, lack of audiometric data, and the fact that the waiting list control group was later in the study reassigned to the treatment groups.

Two group treatment approaches were evaluated by Wise et al. (Wise, Rief, & Goebel, 1998), in 144 in-patients, admitted in a psychosomatic clinic and allocated to a specialised tinnitus ward. Participants were randomly assigned to either a standardized tinnitus management group therapy (TMT) (N=76), including cognitive therapy, attention diversion techniques, and lifestyle education, or to a more general problem-solving group therapy (PS) (N=68). The duration of both treatments was approximately 7 weeks, and patients rated the treatments (and not their tinnitus) after each session on four dimensions, *perceived help received in dealing with tinnitus, perceived help received in dealing with life problems, the degree to which patients felt understood, and the degree to which they felt being treated properly*, using a VAS for each dimension. *Tinnitus annoyance* was measured with the TQ. The TMT group was rated significantly higher on all 4 dimensions as compared to the PS group. Both groups improved equally well in tinnitus annoyance. Drawbacks are; there were significant baseline differences between the groups, patients received additional treatments in both groups, dropout in the PS group was larger, and lack of follow up data.

Three forms of group therapy approaches were compared by Kröner-Herwig et al (Kroner-Herwig, Frenzel, Fritsche, Schilkowsky, & Esser, 2003). Patients (N = 96) were randomly assigned to a CBT based Tinnitus Coping training (TCT), a Minimal Contact-Education group (MC-E), a Minimal Contact-Relaxation group (MC-R), or to a waiting list control group, and were assessed at pre- and post treatment. Outcomes included a *tinnitus diary ratings*, *tinnitus* *severity*, *tinnitus disability*, *tinnitus coping*, *number of more general complaints*, *depression*, and *self reported change in well-being*. When comparing the TCT group to all other groups, significant improvements, in subjective loudness, awareness, control, coping, tinnitus-disability, and wellbeing, were found. MC-E and MC-R did not differ from each other, but MC-E did slightly better in improved well-being and MC-R in reduced disability, when compared to the WLC. The effects from post-treatment to follow up 1 and 2 in the TCT group were significantly reduced in applying relaxation and perceived control over tinnitus. All other effects remained stable over time. Limitations of this study include the lack of follow up in the control conditions, the clustering of the outcomes, providing no insight into the changes on the outcomes separately, and the large baseline differences between groups, making it hard to interpret results.

In a RCT performed by Zachriat and Kröner-Herwig, 77 tinnitus patients were randomly allocated to a habituation treatment (HT), based on a TRT protocol (Jastreboff, 1999; Kroner-Herwig, et al., 2003) (n=30), a tinnitus coping training (TCT) (n= 27) based on cognitive behavioural principles and relaxation therapy, or to a control group (n=20) who received one single educational session (EDU) (Zachriat & Kroner-Herwig, 2004). Measures on a *tinnitus diary* (loudness, hours of tinnitus awareness, subjective control of tinnitus), *tinnitus severity*, *tinnitus coping*, *tinnitus catastrophizing*, *dysfunctional cognitions*, *TRT questionnaire*, *subjective success*, *general complaints*, and *psychological disorders* were taken at baseline and 6 follow ups, although assessment varied per measurement and per group, including a combination of, but not all of the measures at the different time points and within the different groups. Improvement in general well being and adaptive behaviour was greater in the TCT than in the HT group. Both groups showed significant improvements compared to the EDU group, in tinnitus severity, disability and diary ratings. In general it was concluded that though both TCT and HT did fairly well over time, TCT showed more benefits at follow up. Noteworthy is that the majority of patients in the HT group did not use sound generators and received extensive group counseling only, probably explaining the positive effects in this group. Other drawbacks include: outcomes were clustered in the analyses, missing measurements on outcomes, missing measurements in treatment conditions, incomplete data on follow ups.

Hiller and Haerkötter (Hiller & Haerkötter, 2005) investigated whether sounds stimulation has an additive effect on CBT. Outpatients (N=124) were randomly assigned to 2 different CBT groups, both with and without a white noise generator (NG). Patients improved from baseline to post treatment, to 6 and 18 months follow up on *tinnitus severity*, *dysfunctional cognitions and beliefs*, tinnitus diary ratings on *loudness*, *unpleasantness*, *general mood*, *perceived control*, *general complaints*, *hypochondriac attitudes/behaviours*, and *dysfunctional psychosocial functioning*, irrespective of wearing NG's. Limitations include; missing follow-up measurements on some of the outcomes, and probable confounding co-morbidities.

Henry et al (Henry, et al., 2006b) were interested in whether TRT counseling only (without the sound therapy), would have beneficial effects as well. These researchers randomly assigned 269 tinnitus patients to one of three groups; a TRT educational group (with and without sound therapy), a traditional support group, and a no-treatment control group. *Tinnitus severity* decreased significantly over a period of 6, as well as 12 months, within the TRT educational groups, with no benefits for the other groups. Authors concluded that educational sessions without specific sound therapy, as is prescribed by TRT, are in itself an effective intervention. Noteworthy limitations include the predominantly male veteran sample, the possible confounding of hearing, since this was not controlled for in outcome analyses, and the use of only 1 outcome measure.

Discussion

In conclusion, currently multidisciplinary treatment approaches in tinnitus management are highly diverse, are usually a combination of different treatment elements, and tinnitus diagnostics and outcome assessments differentiate not only across the different research approaches but as well across different clinical settings. More often than not studies are hardly comparable, very low in methodological quality, thereby exhibiting low level of evidence. Through the years several reviews have been conducted, and whether scoping reviews, reviews of treatment approaches, or meta-analytical reviews of RCT's (see table 1 for a summary of selected reviews), up until now they all reach similar conclusions as are described above.

In a scoping review of psychological tinnitus treatments (Andersson, Melin, Hägnebo, Scott, & Lindberg, 1995) studies were reviewed and classified by its most salient psychological treatment feature (since all were combinations of treatment elements). It was concluded that offering cognitive behavioural coping techniques in combination with relaxation exercises received the most empirical support, though methodological quality of the studies was considered too low, outcomes of the different studies were not comparable, and treatment elements within a category as well as the combinations of treatment elements vary widely. In a literature review by Dobie in 1999, it was concluded that on 53 reports of randomised clinical trials on tinnitus treatments none of the RCT's provide conclusive proof for long-term reduction in tinnitus annoyance or impact, in excess of placebo effects, there was a lack of consensus regarding therapeutic outcome across the trials, and measurements of acoustic characteristics (i.e. loudness and pitch) are poorly correlated with tinnitus severity and therefore poor outcome choices (Dobie, 1999). A meta-analytical review of psychological treatments (Andersson & Lyttkens, 1999b) suggested that psychological treatments were effective, though the number of included studies was rather small, low in power and across studies outcomes were heterogeneous. Noteworthy about this study is that, though authors aimed to evaluate psychological treatments only, treatment was almost always a combination of several elements (not only psychological). Martinez-Devesa et al. (2010) performed a meta-analytical study to assess whether cognitive behavioural therapy (CBT) for tinnitus is an effective treatment approach. It was found that CBT is effective in decreasing tinnitus severity and negative mood, when compared to other no treatment or forms of treatment. Again, no effects were found on measures of acoustic characteristics of tinnitus (i.e. loudness and pitch) (Martinez-Devesa, Perera, Theodoulou, & Waddell, 2010). In a more recent review about the effectiveness of TRT (Phillips & McFerran, 2010) only one single RCT was of sufficient quality to include, which showed that TRT, including the counseling, indeed was more efficient when compared to only auditory masking, as was found on tinnitus specific measures. However, the author emphasizes that the single trial was of low quality and conclusions have to be considered tentatively. Hobson et al. (2010) performed a systematic review of RCT's on the effectiveness of sound therapy by sound generators (including hearing aids). Efficacy of sound therapy in tinnitus management was not established on changes in tinnitus loudness, severity of complaints or quality of life ratings. Authors concluded there is a lack of quality, standard outcome measures, follow-up data, and a high risk of bias in results (Hobson, Chisholm, & El Refaie, 2010). A more recent meta analysis, including only randomized controlled trials of cognitive behavioural therapy (CBT) for tinnitus distress (Hesser, et al., 2011) showed that CBT was significantly more effective on tinnitus specific measures, as compared to a no treatment control group or an alternative treatment, and effects seem to remain over time. They conclude once more that most trials were too small scale, and incorporated low quality of methodology. Finally, a meta-analysis of randomized controlled trials, examining existing level of evidence for more general tinnitus management strategies (Hoare, et al., 2011) resulted in evidence for CBT-based strategies for tinnitus once more, though a lack thereof for the use of hearing aids, sound generators, sound based therapies, and TRT. Authors come to similar conclusions in that in general studies are of low power, report incomplete data, and exhibit low levels of evidence, but that a CBT-based approach is beneficial when compared to control groups or other forms of treatment.

The high variability in intervention studies, low methodological quality, and high variety in research outcomes, makes it difficult to interpret and synthesise previous data and reach sound conclusions about what multidisciplinary tinnitus treatment approach is effective for whom. However, we can conclude that CBT for tinnitus seems the most promising approach in diminishing tinnitus related distress, severity, disability, negative mood and decrease main complaints of patients, corroborated in both older and more recent reviews

Additionally we can conclude that the multidisciplinary approach has been implemented in almost all studies, combining different treatment elements, and support has been found in 1 study (El Refaie, et al., 2004) for its effectiveness in increasing general quality of life. The use of sound therapy with sound generating devices, whether masking devices, wearable players or hearing aids, has not been proven to be effective as a single treatment approach, as have been corroborated by recent meta studies. Even when combined with counseling sessions (as is the case in TRT based approaches), the effects seem very modest at best. Usually the lack of evidence and low methodological designs of the studies about sound-based approaches have been pointed towards as being the reason for insufficient evidence so far.

Based on the current review in combination with findings of other reviews, we suggest that the treatment strategy might be best organized interdisciplinary, using a stepped care approach (Von Korff & Moore, 2001), whereby health care is provided by multiple disciplines together, gradually increasing intensity of treatment in steps, so the larger part of the patients can be treated effectively with a fairly short intervention (diagnostics and information), and additional treatment steps can be indicated for those suffering on a more severe level (the more intensive CBT approaches, preferably in groups). In order to assess the level of tinnitus suffering, and to allocate more resources when needed, we suggest to incorporate, next to audiological measurements, a general measure of tinnitus severity, tinnitus related impairment in daily life, as well as assessment of cognitive functioning and emotional distress both general as well as tinnitus specific. By using a stepped care multidisciplinary approach, standard essential medical/audiological diagnostics and information can be provided easily to a large part of the patients, giving opportunity to indicate more severe levels of tinnitus distress, and allocate additional recourses and more intensive and costly treatment approaches there were needed most. Additionally, growing evidence suggests that an overall CBT based framework in tinnitus management is advisable; moreover, almost all studies included some form of education, information and/or counseling for the patients, to foster cognitive restructuring of patient's beliefs and attitudes. Finally, fragmented treatment strategies, providing treatment elements serially and often at random, are expected to lead to unwanted increase of health utilization, costs and more importantly prolonged suffering of the patient. Unfortunately, current usual practice in tinnitus treatment still seems to be fragmented and highly diverse within countries, settings and within the disciplines involved, without standardized guidelines for diagnostics, treatment, and outcome assessments. (Cima, et al., 2012; Hoare, et al., 2012)

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APPEMDIX Summary of characteristics of included studies

Study	Sample	Design	Interventions	Measurements	Outcomes[1]	Results[2]	Limitations
Lindberg, Scott, Melin & Lyttkens, 1988	N=75 adults with moderate to severe tinnitus 57% male Mean overall age 53.9	Follow up repeated measures design with 3 mo fu[3]	Audiological measurements/counseling Tinnitus information/education Ca. 10 individual 1-hour behavioural treatment sessions *(Progressive relaxation, tinnitus-cognitive control techniques)*	4 measurements: pre- during- 2 wk[4] fu 3mo[4] fu	A tinnitus diary; tinnitus-discomfort &mood (1 wk) A tinnitus interview (t0 & 3 mo fu) Tinnitus matching[5] (before treatment and at 3 mo fu)	Strong positive effects (pre- to 2 wk fu) discomfort & mood. (p<.001) 74% patients improved (interview) No significant reductions tinnitus loudness /pitch	no control or alternative treatment control group missing measurements on 2 of the outcomes the individual behavioural treatment varied in amount of sessions and contents across patients
Andersson, 1997	N= 69 adult tinnitus patients 53,6% male Mean overall age 55.3	Descriptive case study 4 groups	Patients categorized in 4 groups acc. to salient previous treatment No treatment (n=24) Acupuncture (n=19) Relaxation (n=13) Other treatments (n=13)	1 measurement	Tinnitus Questionnaire (TQ) shortened	Minor differences between groups. Untreated group more acceptability for change (P<.05)	All patients received more than one previous treatments, only most salient was reported No pre-treatment data
El Refaie, Davies, Kayan, Baskill, Lovell, Owen, 2004	N= 57 adult tinnitus patients (and their families) Percentage of males unspecified Mean overall age 62,0	Follow up repeated measures design with 1 yr fu	2 stepped-care Step 1: Medical/audiological diagnostics, intervention, and counseling Step 2 Psychological individual therapy: CBT, Problem-solving, general counseling Audiological counseling: Relaxation, tinnitus control, follow up on sound/hearing devices.	2 measurements Pre- clinic Post- clinic	Tinnitus measure (tinnitus characteristics, hearing aid use, tinnitus severity and annoyance) Quality of life, Short form 36 (SF-36) Quality of family life (questionnaire with 30 items assessing family's view on changes as a result from tinnitus	Reduction tinnitus annoyance Improvement functional & social handicap, general quality of life (P<.01). Improvement Quality of family life (n.s.[6]) Patients (hearing aids) (18%) improved social & functional handicap Patients(noise generators) (25%): no improvement disability/handicap	No data on effectiveness of step 1 only vs. additional step 2 care /No between group comparisons No data on how many patients received step 2 Periods in between measurements undefined Treatment (clinic attendance) very broad range of treatment elements
Herraiz, Hernandez, Plaza, Santos de los, 2005	N=158 adult tinnitus patients 44% males Mean overall age 53 N=68 TRT with sound generators (PAG) N=68 TRT only counseling (RCG) N=21 waiting list control	Non-randomized clinical trial	TRT RCG: medical /audiological diagnostics, education/ counseling TRT PAG: medical/ audiological diagnostic, education/counseling, sound generators PTG (partially treated group, refusing prosthesis, though indicated) WCL medical/audiological diagnostics only	3 measurements Pre- 6-mo fu 12- mo fu	Question: Do you feel better, same or worse? VAS: tinnitus intensity, annoyance Tinnitus disability (Tinnitus Handicap Inventory (THI))	82% RCG&PAG improved compared to WLC & PTG (p<.05) Tinnitus intensity &annoyance improved RCG&PAG compared to WLC (P<.05) but not to PTG Tinnitus disability improved in RCG&PCG compared to WLC (P<.05)	Subjects were not randomly assigned to the groups Significant group differences at baseline on THI and VAS

	N=21: partially treated group (PTG)					No additional treatment effect for sound generators.	
Henry, Schechter. Zaugg, Griest, Jastreboff. Vernon, Kaelin, Lyons, Stewart, 2006	N=123 severe tinnitus suffering US veterans 95% males Mean overall age 59,8 N=59 tinnitus masking Group (TM) N=64 tinnitus retraining group (TRT)	Non-randomised clinical trial	TM: 5 counseling sessions (4hrs), sound generators adjusted at patients comfort level TRT 5 counseling session (6hrs) Sound generators adjusted just below the mixing point (tinnitus maintains perceivable) Attention diversion, focus on environmental sound, neurophysiological model	5 measurements Baseline 3-mo 6-mo 12-mo 18-mo	Tinnitus handicap inventory (THI) Tinnitus Handicap Questionnaire (THQ) Tinnitus Severity Index (TSI)	Severe sufferers improved in both groups improved (p<.05) on all measures, Better result for the TM group after 3 mo, and better results for the TRT group after 6, 12 and 18 mos Very severe suffering is reduced more in TRT than in TM, over a period of 18 mos.	Biased allocation Not representative study sample (veteran males) Long treatment period Hearing loss not controlled for No follow up data TRT group received more hours of structured counseling TM and TRT carried out by 1 specialist in the respective fields
Lindberg, Scott, Melin & Lyttkens, 1989	N= 27 adult tinnitus patients 48% male mean overall age 55.3 N=9 Relaxation exposure group (RE) N=10 Relaxation distraction group (RD) N=8 Waiting list control (WLC)	RCT 2 groups 1 WLC	*Before randomization* Audiological measurements/ counseling Tinnitus information/ education *Randomization RE or RD* RE: 10 1hr sessions, 2-3 wks: behaviour analysis, progressive, quick, and differential relaxation; last 4 sessions exposure environmental noise RD: 10 1hr sessions, 2-3 wks: behaviour analysis, progressive, quick, & differential relaxation; last 4 sessions; attention-shifting/distraction training by relaxation (mental images)	3 measurements: Pre- During 2 wk fu	1 wk of daily VAS recordings while exposed to sound on subjective loudness of tinnitus, discomfort, and controllability, tinnitus matching (only pre and post treatment) Questionnaire (not specified, and only measured at fu)	Main effect on VAS self-recordings from pre treatment to fu only when combining RE & RD, as compared to the WLC. (p<.05). No group difference between RE and RD. No significant reductions tinnitus loudness/ pitch	Very small sample Lack of reports on all between treatment-group analyses Lack of reporting SD's[3]. Assessment of loudness non-standardized Treatment groups very similar, both using distraction, missing measurements on 2 of the outcomes
Davies, McKenna & Hallam, 1995	N= 30 adult tinnitus patients 44% male mean overall age 56.3 N=7 Passive relaxation group (PR) N=12 Applied relaxation group (ART) N=11 Individual cognitive therapy	RCT 3 groups	PR (passive relaxation); training for progressive muscle relaxation, and relaxed breathing AR (applied relaxation training): training to apply relaxation techniques to distressing situations caused by tinnitus or sound in general, attention diversion ICT (individual cognitive therapy) identifying maladaptive beliefs and emotions by use of Rational Emotive Therapy (RET) and the	4 measurements: Pre- post- 1 mo fu 4 mo fu	Tinnitus loudness and annoyance (5 pt Likert) Tinnitus Questionnaire (TQ); *Distress due to tinnitus/tinnitus severity* Beck Depression Inventory (BDI) State Trait Anxiety Inventory (STAI) Daily ratings of	*(PRT omitted from statistics)* No improvement loudness/annoyance AR & ICT pre-post treatment effect on TQ (p<.05), no group differences, no 4 mos fu effects Both AR and ICT reduced depression (p<.5) Both AR and ICT reduced anxiety at 1 mo fu (p<.05)	small sample size no data on audiometry/hearing impairment PR group omitted from analyses not all of the outcomes were measured baseline differences effects of use of sound generators was not evaluated

	(ICT) *Across groups n=16 sound-generators*		Socratic dialogue.		loudness, annoyance and insomnia Independent assessor's clinical rating	No effects on loudness, annoyance, insomnia 69% of patients tolerated tinnitus post treatment	
Kröner-Herwig, Hebing, Van Rijn-Kalkmann, Frenzel, Schilkowsky & Esser, 1995	N= 43 adult tinnitus patients 60.5% male mean overall age 47,3 N=15 cognitive behavioural group therapy (TCT) N=9 yoga group training (yoga) N=19 waiting list control condition (WLC)	RCT 2 groups 1 WLC	TCT (10 X 2h group sessions); education, stressor-analysis, progressive relaxation, attention training, cognitive coping techniques Yoga (10 X 2h group sessions): exercises for relaxation, adequate body perception, breathing	3 measurements: Pre- Post- 3 mo fu	Audiometry & Tinnitus matching procedure A tinnitus diary on loudness, discomfort, sleep, interference, control, hrs ignored Tinnitus questionnaire (TQ) General measure of well-being,/General measure of depression	No between group differences tinnitus acoustic characteristics Significant effects TCT compared to Yoga and WLC in self-efficacy and control and decrease in worry/disturbance from tinnitus (P<.05) Tinnitus distress decreased in all treatment groups compared to WLC (P<.05) Improvement in wellbeing/mood in TCT when compared to WLC (P<.05)	Effects on non-standardized measures WLC group was reassigned to treatment groups no data on audiometry/hearing impairment Lack of reporting SD's.
Wise, Rief & Goebel, 1998	N= 144 adult tinnitus in-patients 60.4% males Mean overall age 50.3 N=76 tinnitus management group therapy (TMT) N=68 problem solving group therapy (PSG)	RCT 2 groups	TMT (10 X 100min) cognitive strategies, attention diversion, lifestyle education PSG (10 X 100min) working on general life problems	2 measurements Pre- Post- VAS After each therapy session	Tinnitus Questionnaire (TQ) (pre- and post-treatment) VAS-scales to measure patients rating on: perceived help for dealing with tinnitus perceives help for dealing with life problems Degree of feeling understood Degree of proper treatment	No group differences in decreased tinnitus distress (TQ) both groups improved Patients rated TMT group significantly better on all 4 VAS dimensions (P<.001) Significant baseline difference in tinnitus annoyance (TMT > PSG) P<.05)	Significant baseline differences between groups patients in both groups received additional therapies higher dropout in PSG group lack of follow-up evaluation
Kröner-Herwig, Frenzel, Fritsche, Schilkowsky, Esser,	N=96adults with tinnitus 54,2% males mean overall age 46.8 N=43 cognitive-	RCT 3 groups 1 WLC	TCT group therapy, 11 X 90-120min sessions. Emphasis on: Tinnitus education, relaxation, cognitions, avoidance, emotions, habituation, imagery, attention, distraction, problem-solving,	2 measurements Pre- Post- TCT additionally evaluated at	Tinnitus diary (2 wks at pre, post and fu 1); Tinnitus Questionnaire (TQ): Tinnitus Disability Inventory (TDI)	Pre- post improvements in TCT compared to MC-E, MC-R, & WLC in subjective loudness, awareness, control, coping, & tinnitus disability	No follow up data on MC-E, MC-R, and WLC, no between group comparisons at fu 1 and 2 Baseline differences in groups Analyses were not performed for all outcomes separately;

2003	behavioural coping training (TCT) N=16 minimal contact (MC-E) N=16 minimal contact (MC-R) N=20 waiting list control (WLC)		operant mechanisms, attitudes, maintaining skills MC-E, 20 participants, 2 group sessions: tinnitus education, fears, prognosis & consequences, self-help, group discussion, MC-R, 20 participants, 4 group sessions: relaxation training.: Education, relaxation & distraction, verbal relaxation instructions, discussion of progress and problems	6and 12 mo fu	Coping General complaints (SCL-90) Depression (CES-D) Questionnaire of subjective change Outcomes were pooled into Diary (1) Coping (4) Disability (2, 3) General psychopathology (5,6) Subjective change (7)	Larger subjective change in wellbeing and suffering MC-E and MC-R no difference MC-E more improvements in subjective change, and MC-R in disability, when compared to the WLC At fu 1 and 2 in TCT reduced effects in relaxation and perceived control over tinnitus. All other effects remained stable over time	variables were clustered, and averaged, and used as independents
Zachriat & Kroner-Herwig, 2004	N=77 adults with severe tinnitus (TQ>25) 67 % males Mean overall age 53.8 year N=30 TRT based habituation therapy (HT) N=27 in tinnitus coping training (TCT) N=20 in educational control group (EDU)	RCT 3 groups	HT: 5 X 90-120 min group sessions over a period of 6 mos, freq: 4-6 wks: Education, counseling , sound generator (in 23% of patients only) TCT: 11 wkly group sessions, 90-120 min: Relaxation, attention, distraction., identify cognitive processes and emotional responses EDU: 1 group educational session	7 measurements Pre- Post- 3-mo fu 6-mo fu 12-mo fu 18-mo fu (for HT and TCT) 21-mo fu (for TCT)	A tinnitus diary (1 wk): loudness, hours of tinnitus awareness, subjective control of tinnitus Tinnitus Questionnaire (TQ) Coping with tinnitus (Catastrophizing Dysfunctional cognitions Questionnaire for TRT (at 12 mos) Changes in wellbeing (at 12 mos) Subjective success (at 12 mos) General complaints (SCL-90) (pre- treatment) For fu's outcomes were clustered and no longer used as independents separately	(TCT=HT) > EDU reduction disability (P<.05) (TCT=HT) > EDU positive change of subjective tinnitus parameters (P<.05) Catastrophizing decreases in TCT & HT (P<.05) TCT>HT>EDU coping (p<.05) TCT>HT>EDU annoyance, ability to ignore and influence tinnitus (P<.05) TCT>(HT=EDU) global changes in well-being and adaptive behaviour In HT 2 patients refused the sound generators, 28 started and only 7 chose to wear them throughout the trial. In this group no significant change over time in tinnitus disability	Time allocated to patients differed within groups at fu's outcomes were clustered incomplete fu in treatment conditions not all outcomes were evaluated on use of generators not controlled for hearing loss
Hiller, & Haerkötter, 2005	N=136 adult tinnitus patients N=70 mild to moderate tinnitus in	RCT	TE: 4 X 90min wkly group sessions: aims, homework, education hearing & tinnitus, neurophysiological &coping	4 measurements Pre- Post- 6-mo fu	Tinnitus Questionnaire (TQ) Dysfunctional cognitions and beliefs	Both groups (TE and CBT) improved significantly on measures on tinnitus-related distress,	Quasi randomization Not all outcomes were assessed at every time point Heterogeneous sample (e.g.

	Tinnitus education condition (TE) (34 with noise generators NG, 36 without NG) N=66 severe tinnitus in CBT-condition (33 with NG and 33 without NG) NG in both TE and CBT worn at least 6h every day. Both groups had 8-10 participants		models, avoidance of silence, discussion & questions, noise generators CBT: 10 X 120min wkly group sessions: explanation aims, homework, education hearing &tinnitus, neurophysiological &coping models, avoidance of silence, discussion & questions, cognitive techniques, relaxation, dysfunctional cognitions and behaviours, attention diversion, noise generators	18-mo fu	A tinnitus diary on loudness, unpleasantness, general mood, perceived control (1 wk) General complaints (SCL-90) hypochondriac attitudes and behaviours (Whiteley Index); Dysfunctional Analysis Questionnaire (DAQ) : psychosocial functioning	dysfunctional cognitions, general complaints, depression, hypochondria and psychosocial functioning (P<.05). No between group differences No significant differences were found between the TE or CBT with NG's and without NG's, i.e. no additional value of NG's could be established Tendency of patients without NG improving slightly more	patients with and without hyperacusis, sensitivity to sounds, and hearing loss)
Henry, Loovis, Montero, Kaelin, Anselmi, Coombs, Hensley, James, 2007	N=269 severe tinnitus suffering US veterans 97% males Mean overall age 61.6 N=94 TRT counseling only (TRT-C) N=84 traditional support (TS) N=91 waiting list control (WLC)	RCT 3 groups	TRT-C: 4 X 90 min group sessions education, attention diversion counseling, and group discussions TS: 4 X 90 group discussions WLC: no treatment	4 measurements Baseline 1-mo 6-mo 12 mo	Tinnitus Severity Index (TSI)	Only the patients in the TRT-C group improved in tinnitus severity over a period of 6 and 12 mos (P<.001, e.s. = .45 to .59)	Study sample (veteran males) 1 outcome measure only Hearing loss not controlled for
Andersson, Melin, Hagnebo, Scott, Lindberg, 1995	N= 38 studies	Scoping Review of literature from 1973 till1995	Psychological treatment approaches: hypnosis biofeedback cognitive behavioural approaches relaxation techniques cognitive coping strategies	No selection criteria All studies were included	Outcomes were unspecified	Authors conclude relaxation techniques in combination with some form of cognitive behavioural techniques is most beneficial	low methodological quality of included studies outcomes not comparable high variety in treatments within a category Categorization by most salient treatment element.
Dobie, 1999	N= 69 RCT's	Literature review from 1964 till 1998	Tinnitus therapy approaches N=53 RCT's on tocainide &related drugs, carbamazepine, benzodiazepines, tricyclic antidepressants N=16 RCT's on	Only RCT's were included Studies with waiting list control were excluded	Outcomes were summarized but unspecified	there are no well-established treatments for tinnitus None of the treatments eliminates tinnitus or has long-term beneficial	Studies not comparable because of diversity in outcome measures Small/ inadequate sample sizes no long term results

			miscellaneous drugs, psychotherapy, electric/magnetic stimulation, acupuncture, masking, biofeedback, hypnosis, other non-drug treatments			effects Acoustic characteristics poor outcome measure	
Andersson, Lyttkens, 1999	N=18 studies N=24 therapy samples N= 700 total participants	meta-analytic review of studies from 1966 till 1998	Psychological treatments Cognitive/cognitive-behavioural treatment Relaxation Hypnosis Biofeedback Educational sessions Problem-solving (Studies on sound therapy were excluded)	Included in case of: English language, Scientific papers, Info on sample size & statistics, measurement details, intervention details	Outcomes were categorized in: Loudness Annoyance Negative affect Sleep problems	Weak effects on tinnitus loudness, not maintained at follow up (e.s.^{3} = .009) Moderate effects on tinnitus annoyance (e.s.= .48) Small effects on negative affect (e.s. = .28) Very small effects on sleep (e.s. = .20)	Small number of studies Low power in most of the studies Heterogeneity in outcome measures though clustered in this study Low standard of reporting results Average follow-up period only 5.4 mos
Martinez-Devesa, Perera, Theodoulou Waddel, 2010	N=8 RCT's on CBT N=468 adult tinnitus sufferers	meta-analytic review of studies till May 2010	Cognitive behavioural therapy	RCT's	Outcomes categorized in: Primary: Subjective loudness Secondary: Objective/subjective improvement of mood Quality of life (assessed by tinnitus specific measures THI, TQ and TSI) Adverse effects	CBT is effective on tinnitus specific severity/distress measures CBT is effective in decreasing negative mood No effects of CBT on loudness	Though quality of life measures were said to be considered, instead tinnitus 'severity/distress' measures were considered, which are hybrid assessing not general quality of life but include impact on cognitions, emotions, sleep and hearing.
McFerran, 2010	N=1 RCT on the effectiveness of TRT N=123 adult tinnitus patients US veterans	Systematic review of literature till august 2009	Tinnitus retraining therapy (TRT)	RCT's Excluded: RCT's on pulsatile tinnitus, tinnitus by Otosclerosis, Meniere's, or tumours	Primary: Tinnitus severity/disability Secondary: Tinnitus acoustic characteristics Depression General well-being	In the one study found, TRT was beneficial	Low methodological quality of the one study: Allocation bias Predominantly male US veterans Only severe sufferers
Hobson, Chisholm, El Refaie, 2010	N=6 RCT's on sound creating devices N= 553 adult tinnitus patients	Systematic review of literature till Septemb	Sound based therapy by use of sound-creating devices including hearing aids	RCT's	Primary: Change in loudness Change in overall severity and/or impact in daily life Secondary: Change in thresholds	No change in loudness or severity of tinnitus can be found as a result of sound-creating devices No side effects or adverse events were reported in included studies	No long term data High risk of bias in included studies Lack of homogenous outcomes Low quality of study methodologies

		er 2009			of pure tone audiometry Side effects/adverse effects		
Hesser, Weise, Zetterqvist-Westin, Andersson, 2010	N=15 RCT's on CBT for tinnitus. *(N=10 RCT's on CBT for tinnitus with fu data)* N=1091 adult tinnitus patients	meta-analytic review of studies till September 2009	Cognitive/cognitive- behavioural therapy for tinnitus	RCT's	Tinnitus specific questionnaires Negative mood measures VAS Other, non validated measures	CBT compared to WLC and alternative treatments is effective post treatment as measured with tinnitus specific measures (e.s.=.70 and .44 respectively) Effects were maintained over time (as was seen in the 10 studies with fu data)	Most trials were considered small-scale, and poorly controlled
Hoare, Kowalkowski, Kang, Hall, 2011	N=28 RCT's	meta-analytic review of studies till August 2010	Existing tinnitus management strategies	RCT's	Only validated outcome measures were included	Of the 28 studies 6 were rated low level of evidence, 17 as moderate and 5 as high level evidence. Little or no evidence for effectiveness of hearing aids, maskers, sound based approaches, or TRT was found Moderate effect sizes for CBT was found (e.s. = 21 to .67)	Most studies: lack of power, incomplete data reporting, insufficient level of evidence

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[1] Psychometrically evaluated measures are listed by name and abbreviation, else the construct is mentioned

[2] Significance levels and effect sizes are included, when described in the study

[3] Fu: Follow up; e.s.: Effect size, S.D.: Standard deviation

[4] Wk: week; mo: month

[5] Tinnitus matching includes: tinnitus loudness matching, tinnitus pitch matching, and loudness discomfort level; to assess acoustic characteristics of tinnitus

[6] n.s.: Non significant

CHAPTER III

TINNITUS INTERFERES WITH DAILY LIFE ACTIVITIES: A PSYCHOMETRIC EXAMINATION OF THE TINNITUS DISABILITY INDEX

Based on

Cima, R. F. F., Vlaeyen, J. W. S., Maes, I. H. L., Joore, M. A., & Anteunis, L. J. C. (2011). Tinnitus Interferes With Daily Life Activities: A Psychometric Examination of the Tinnitus Disability Index. *Ear and Hearing, 32*(5), 623-633

Abstract

Objectives: The Tinnitus Disability Index (TDI) is presented as a novel and brief self-report measure for the assessment of the interference of tinnitus with performance in specific daily life activities. We hypothesized that the TDI is a reliable and valid measure and that tinnitus disability is strongly associated with tinnitus severity, subjective tinnitus intensity ratings, and ratings of general health. Design: Six-hundred-and-fifteen tinnitus patients from across the Netherlands completed online a number of questionnaires about their tinnitus, their general health and demographics. Two samples were extracted by a random-split: Sample I (N=311) for exploratory factor analysis and sample II (N=304) for confirmatory analysis, using structural equation modelling. One-hundred-and-forty-three of the first included respondents repeated assessment after a 2-week time interval, for test/re-test analysis. Regression analyses were employed to investigate construct validity. Results: Present analyses reveal that tinnitus disability, as measured with the TDI might be best understood as a single component construct, i.e. one single underlying factor. The TDI is reliable over time and tinnitus related disability, as measured with the TDI, is strongly associated with subjective ratings of tinnitus intensity, negatively associated with quality of life ratings, and distress due to tinnitus. Conclusions: The TDI is a brief and easily administered index measuring a unique construct, namely the experienced interference of the tinnitus with daily life activities, which is invaluable in the assessment and treatment of tinnitus patients.

Introduction

Tinnitus can be defined as the continuous perception of a sound without the presence of an external source. It has also been described as phantom auditory perception (Jastreboff, 1990) and mostly ringing, beeping or buzzing sounds are reported. Tinnitus is perceived at least once in life by 30% of the general population. It has been estimated that up to 15% of the general population perceives tinnitus constantly, and 6% - 25% of this group suffers from it on a daily basis (Heller, 2003). Severe tinnitus suffering has been associated with: audiological dysfunction (hearing loss, hyperacusis), psychological distress (anxiety, depressive symptoms), cognitive dysfunction (disorders in attention and concentration), and characteristics of the tinnitus sound (loudness, pitch) (Andersson, 2003; Hiller & Goebel, 2006; Holgers, Zoger, & Svedlund, 2005). A uniformly legitimate underlying cause has of yet not been discovered (Noble & Tyler, 2007), and different assessment strategies and treatment approaches for chronic tinnitus exist (Jastreboff & Hazell, 1993; Martinez Devesa, Waddell, Perera, & Theodoulou, 2007; McCombe, et al., 2001; Zachriat & Kroner-Herwig, 2004). Reliable instruments (questionnaires, structured interviews), rating scales and audiometric protocols have been developed (Heller, 2003; Hiller & Goebel, 2006; McCombe, et al., 2001; Tyler, Aran, & Dauman, 1992) to assess these factors for it is known that these are the main contributors to the poor general health and functional disturbances in tinnitus sufferers (Erlandsson & Hallberg, 2000; Meikle, et al., 2007).

In a recent review on disease specific health related quality of life (HR-QoL) instruments used to measure outcomes in tinnitus trials, six commonly used HR-QoL tinnitus instruments were identified (Kamalski, Hoekstra, van Zanten, Grolman, & Rovers, 2010; Meikle, et al., 2007). The Tinnitus Handicap Inventory (THI) (Newman, Jacobson, & Spitzer, 1996) has three subscales; functional, emotional, and catastrophic responses to the tinnitus. Both overall and subscale internal consistency were found to be good. The Tinnitus Questionnaire (TQ) (Hallam, McKenna, & Shurlock, 2004) has six domains; emotional distress, cognitive distress, intrusiveness, auditory and perceptual difficulties, sleep disturbances, and somatic complaints as a result of the tinnitus. The TQ items are internally consistent; the subscales lack internal consistency however. The Tinnitus Reaction Questionnaire (TRQ) (Wilson, Henry, Bowen, & Haralambous, 1991) measures distress related to tinnitus and incorporates four domains: general distress, interference, severity, and avoidance of the tinnitus. The focus of these three latter questionnaires is mainly on measuring patient's perception on impaired individual functioning or specific functions as a result of the tinnitus. The Tinnitus Severity Index (TSI) (Meikle, Griest, Stewart, & Press, 1995) is a unified measure for tinnitus severity. Two items specifically address the interference of the tinnitus in daily life activities. The Tinnitus Handicap Questionnaire (THQ) (Kuk, Tyler, Russell, & Jordan, 1990; Meikle, et al., 1995) assesses patient's perceived degree of handicap due to tinnitus. The THQ has three domains; 1) physical health/emotional status/social consequences, 2) hearing and communication, and 3) personal viewpoint on tinnitus. Seven items specifically address the interference of the tinnitus on daily activities; four of which address hearing difficulties, two items address social interactions and one item addresses sleep difficulties because of the tinnitus. The THQ subscales fails on internal consistency. The Tinnitus Severity Questionnaire (TSQ) (Coles, Lutman, Axelsson, & Hazell, 1991), a short unified measure, with two items specifically addressing interference of the tinnitus, one item on sleeping habits and one on impairment in concentration. Table 1 lists these six instruments along with their characteristics and psychometric quality.

The above mentioned instruments were developed to assess tinnitus suffering or burden for clinical discriminative purposes, and are commonly used to evaluate clinical trials in tinnitus research. None of them have been validated on test responsiveness yet. All of the six instruments incorporate items assessing emotional and attentional impairment because of the tinnitus, and questions about hearing difficulties and impaired social interactions are often included as well. Three of the six specifically address the interference of the tinnitus on specific daily life activities. Interestingly, an assessment of the impact of tinnitus on daily life, or the interference of the tinnitus with specific daily life activities without the confounding of emotional, physical or attentional dysfunctioning, has not yet been developed.

Chronic tinnitus is experienced not only as aversive; it also interferes with daily life activities, possibly due to the attention-grabbing nature of the tinnitus. It has been suggested that the characteristics of the tinnitus sound in combination with the psychological make-up of the individual are the main factors contributing to tinnitus annoyance (Tyler, et al., 1992). Others have indicated that interference of the tinnitus is primarily associated with deficits in attentional and memory processes (Andersson & McKenna, 2006; Stevens, Walker, Boyer, & Gallagher, 2007) and that only weak associations exist between tinnitus annoyance and tinnitus characteristics (i.e. loudness, pitch) (Andersson, 2003; Jastreboff & Hazell, 2004). Studies in other research areas have also shown that the level of disability in chronic disease is weakly associated with stimulus intensity. Chronic pain patients, for example, do not differ in their reported pain-intensity from individuals with chronic pain who are not seeking health care, but do differ in the extent to which the pain is disabling in daily life as was reflected in the levels of distorted cognition, pain-related distress, and activity levels (Reitsma & Meijler, 1997).

In accordance with previous findings about parallels between chronic pain and chronic tinnitus (Folmer, Griest, & Martin, 2001; Tonndorf, 1987) it is currently hypothesized that disability measures assessing chronic pain might be similarly relevant in assessing tinnitus-related disability. The Tinnitus Disability Index (TDI) is presented as a self report measure for disability due to tinnitus on daily life activities. An advantage of the TDI is that it is a brief and easily administered instrument, assessing functional disability on 7 intelligible life domains.

The TDI is modelled after the Pain Disability Index (PDI), which was developed as an inventory of pain-interference in daily life. The PDI has shown to be a reliable, valid and brief measure for pain-related disability (Tait, Chibnall, & Krause, 1990). The factor structure of the PDI has been frequently investigated and both a one-factor and two-factor structure has been suggested. The two-factor solution indicates that the PDI assesses disability due to pain in two separate activity categories; Voluntary activities (Family/home responsibilities; Recreation; Social activity; Occupation; and Sexual behaviour) and obligatory activities (Self-care and Life-support activity) (Gauthier, Thibault, Adams, & Sullivan, 2008; Gronblad, et al., 1993; Jerome & Gross, 1991; Tait & Chibnall, 2005).

The purpose of the present study was first to investigate the psychometric properties of the TDI. Reliability, validity and factor structure of the TDI were assessed in a cross-sectional data set of people suffering from tinnitus. It is hypothesized that the TDI has a similar underlying factor structure as has been previously suggested for the PDI. Second, it was expected that tinnitus disability, as measured with the TDI, would be associated with tinnitus-related distress, subjective tinnitus intensity ratings, and ratings of general health, but that correlations amongst these variables would be modest.

Methods:

Participants

Participants were recruited via an advertisement on the websites of the Dutch Association for hearing disorders (www.nvvs.nl) and the Dutch Tinnitus Platform (www.tinnitus.nl). The latter is an organization uniting tinnitus healthcare professionals. Respondents were included in the study in case they were able to hear a continuous tinnitus at the moment; either bothersome or not. Respondents (N=791) from across the Netherlands were included from November 2008 until April 2009. Data from 615 participants were used in current analyses, since there was 22% primary non-response (n=176). The primary non-responders were individuals who registered for the current study but refrained from eventual participation. By using a random split method two samples were extracted from the larger sample. Sample I (N=311) was used to perform an exploratory factor analysis, while confirmatory analysis was performed on sample II (N=304). To investigate test-retest reliability of the TDI, 250 respondents were asked to complete the assessment battery for a second time two weeks later, of which 143 complied. Finally, construct validity was investigated by using a second subsample (N= 382) of individuals who also rated the experienced intensity of the tinnitus sound.

Procedure

A special website was developed to provide additional information about the study and for registration purposes. Participants could enter the study by filling in name, telephone number and email address on a special page on the Website of Maastricht University. They were contacted subsequently and after informed consent was obtained personal log-in codes were sent by email. These codes gave participants access to an internet based electronic environment named 'Emium' (Janssen, 2008) enabling completion of the battery of tests online. Participants were able to log out if necessary and log in again at a later time, but were requested to start the test within a week and to complete the test within one day. Respondents who were not able to complete the questionnaires on-line were enabled to fill them in on paper off-line, by sending copies of the questionnaires by postal mail with a free return-address envelope. The order of administration of the tests was fixed; participants were not able to change the order in which the questions were presented. Each new questionnaire was presented with a clear beginning and end, always starting with an instruction for this particular questionnaire and ending with thanking the participant and a message that the next questionnaire would start. The research protocol was approved by the ethical board of the faculty of Psychology and Neuroscience of the Maastricht University.

TABLE 1. CHARACTERISTICS AND PSYCHOMETRICS OF EXISTING TINNITUS HR-QOL INSTRUMENTS

Instrument	Items	Scoring	Construct validity	Reliability (test re-test)	Subscales
Tinnitus Handicap Inventory (THI)	25	(0) never, (2) sometimes, (4) yes	+	+	functional, emotional, catastrophic responses
Tinnitus Questionnaire (TQ)	52	True Partly true Not true	+	+	emotional distress, cognitive distress, intrusiveness, auditory perceptual difficulties, sleep disturbance, somatic complaints
Tinnitus Reaction Questionnaire (TRQ)	26	(0) not at all (4) almost	+	+	general distress, interference, severity, avoidance
Tinnitus Severity Index (TSI)	12	(0) never (4) always	_	+	none
Tinnitus Handicap Questionnaire (THQ)	27	(0) strongly disagree, (100) strongly agree	+	+	physical health/emotional status/social consequences, hearing and communication, personal viewpoint
Tinnitus Severity Questionnaire (TSQ)	10	0 (not affected), 4 (always affected)	_	_	none

Measures

The assessment battery consisted of the TDI, the Tinnitus Questionnaire (TQ) (Baguley, Humphriss, & Hodgson, 2000; McCombe, et al., 2001), Tinnitus intensity ratings on visual analogue scales (VAS) and a questionnaire about demographics.

Disability due to tinnitus was assessed by the TDI, an adapted version of the Pain Disability Index (PDI) (Tait & Chibnall, 2005; Tait, et al., 1990) consisting of 7 items corresponding to 7 major aspects of daily life: Family/home responsibilities; Recreation; Social activity; Occupation; Sexual behaviour; Self-care; Life-support activity (see Appendix A). Each of these 7 scales is rated on a horizontal numerical scale (0–10) with the following anchors; 0 corresponds to “no disability,” and 10 is equivalent to “total disability”. The advantages of the TDI, as compared to existing measures is that it is concise, easily administered and interpreted, and scores are expected to serve as a valid index for the extent to which tinnitus represents a problematic factor in an individual’s daily life.

Distress caused by the tinnitus or tinnitus severity was assessed by the Tinnitus Questionnaire (TQ). The TQ consists of 52 items rated on a 3-point scale and assesses the psychological distress associated with the tinnitus. Items cover a broad range of negative psychological consequences, auditory perceptual difficulties, sleep disturbances and somatic complaints as a result of tinnitus. Psychometric properties of different language versions of the TQ have shown to be satisfactory in different languages (Baguley, et al., 2000; McCombe, et al., 2001). The internal consistency of the TQ in the current sample was excellent (Cronbach’s alpha = .94 (total sample); .94 (Sample I); .94 (Sample II))

Quality of life was assessed by the Short Form – 36 (SF36) (Hays, Sherbourne, & Mazel, 1993; Mosges, Koberlein, Erdtracht, Klingel, & Group, 2008; Ware, et al., 1998), which comprises 36 items to assess various aspects of quality of life and eight subscales can be calculated; physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. Two general subscales can be derived from the eight subscales: physical and mental health. The internal consistency of the SF36 was excellent (Cronbach’s alpha of the 8 subscales ranged from .83 to .94 (total sample); and Cronbach’s alpha (total score) = .94 (Sample I); .94 (Sample II)). The SF36 has been used before in comparative studies in the hearing disabled population and possesses good discriminant validity (El Refaie, et al., 2004; Mosges, et al., 2008).

Tinnitus intensity was assessed by 3 Visual Analogue Scales (VAS). The VAS intensity ratings were included to assess subjects ‘worst’, ‘least’ and ‘usual’ tinnitus ratings. The following three questions were rated: “How do you judge the intensity of your worst tinnitus?”, “How do you judge the intensity of your mildest tinnitus?”, and,” How do you judge the intensity of your tinnitus in general over the past few days?” The Visual analogue scales were provided with the anchors: ‘not intense at all’ and ‘the most intense sound imaginable’. The Tinnitus Intensity VAS showed good internal consistency (Cronbach’s alpha =.82 (total sample); .81 (Sample I); .82 (Sample II))

Demographics were assessed by a separate questionnaire including questions about age, gender, education, duration of complaints, hearing loss, health care history, current treatment, professional life and sick leave history.

Statistical procedures

Multivariate outliers were identified through Mahalanobis distance ($p < .001$). Three cases of Sample I and 2 cases of Sample II were found to be outliers and were deleted. Both samples contained cases with missing responses on the TDI. Since this is the measure under investigation, 4 cases from Sample I and 3 cases from Sample II with missing data on the TDI were excluded from further analysis. In order to perform exploratory analysis a principal component analysis was carried out on the calibration sample (Sample I) to assess factor structure, using SPSS 15.0 for Windows (SPSS, 2009). To perform the confirmatory analyses structural equation modelling (SEM) was employed using AMOS version 17.0 (Arbuckle, 2006) on the validation sample (Sample II). Second, internal consistency of the TDI was assessed on the total sample (N=609). Third, test-retest reliability of the TDI was investigated using data from a subsample of participants who were invited to complete the battery of tests once again, with a mean interval of 4 weeks (N=146). Fourth, possible differences in demographic properties were investigated first using parametric and non-parametric methods. Fifth, construct validity was examined using Pearson correlation coefficients amongst the measures of tinnitus disability (TDI), tinnitus severity (TQ), and quality of life (SF36). Finally, stepwise regression analyses were carried out with tinnitus disability as the dependent variable and socio-demographics, distress due to tinnitus, tinnitus intensity, and general quality of life as independent variables.

Results:

Participants

In order to investigate whether the two samples differed in demographic characteristics a series of parametric (Age, Employment) and non-parametric (Gender, Marital status, Educational level, Tinnitus duration/location, Hearing disorder) were performed. The two samples were not significantly different in age (*T (285) =-.085, p =.93)* and employment status (*T (285) = .174, p = .86),* and not in distributions in gender, marital status, educational level tinnitus duration/location and hearing disorder ($X^2 \leq 3.2$, $p \geq .08$). Table 2 displays demographic data of both samples.

Exploratory Factor Analysis

A principal component analysis on the 7 items of the TDI from the calibration sample was performed. Only 1 factor was found matching the Eigenvalue = 1 criterion. Consequently rotation was not performed. The 1-factor structure accounted for > 60% of total variance and the KMO measure of sampling adequacy was considered to be excellent (.87).

Since previous results in pain research showed a 2-factor solution of the PDI, a second principal component analysis was performed on the calibration sample, in which 2-factor solution was forced. The two factors were internally consistent; the KMO measure of sampling adequacy was, again, considered to be excellent (.90). Since both factors were allowed to somewhat correlate, oblique rotation was performed resulting in the factor loadings from the pattern matrix. The 2-factor solution accounted for 72% of total variance. Factor 1 accounted for 62.13% (Eigenvalue = 4.35) and factor 2 for 10.49% (Eigenvalue = .74) of the total variance. Table 3 displays the factor loadings of both the 1 and 2 factor solutions. Surprisingly, inspection of loadings shows the first factor to include the first 4 items of the TDI instead of the expected 5 first items assessing voluntary activities in the PDI, and the second factor included the last 3 items, instead of the last two items reflecting obligatory activities in the PDI. These results might indicate a slightly different underlying factor structure in tinnitus disability as measured with the TDI in tinnitus patients as compared to pain disability as measured with the PDI in chronic pain sufferers. The intercorrelation between both factors was relatively high (Pearson r = .61, p = .000).

TABLE 2. DESCRIPTIVES OF SAMPLE I (CALIBRATION SAMPLE) AND SAMPLE II (VALIDATION SAMPLE)

SAMPLE		I		II				I		II	
Total N		311		304				311		304	
Outliers		3		2				3		2	
Missing	(Deleted list wise)	4		3				4		3	
N		304		299				304		299	
Mean age (SD)		51.5 (11.6)		51.3 (12.5)				51.5 (11.6)		51.3 (12.5)	
		N	%	N	%			N	%	N	%
Gender	Male	185	61	171	57	Employment	Yes	189	62	187	63
	Female	119	39	128	43		No	115	38	112	37
Duration	> 1 year	36	12	31	10	Location	Left	71	23	64	21
	1 > 5 years	111	37	104	35	Tinnitus	Right	39	13	50	17
	5 > 10 years	61	20	52	17		ADS	153	50	146	49
	10 years <	96	32	112	37		Middle	41	13	39	13
MS	Single	38	12	42	14	HL	Yes	139	46	149	50
	LT	42	14	39	13		No	165	54	150	50
	Married	199	65	197	66	Location HL	Left	38	27	38	26
	Divorced	20	7	20	6		Right	15	11	27	18
	Widowed	5	2	1	1		ADS	86	62	84	56
Education	Prim/sec	6	2	7	2	Treatment	ENT	19	27	16	27
	High school	100	33	103	34		GP	4	6	2	3
	Intermediate	63	21	64	21		AC	25	35	20	33
	Higher	135	45	125	42		PT	2	3	2	3
Current treatment	Yes	71	23	60	20		Other	21	30	20	33
	No	233	77	239	80						

MS = Marital status; LT = Living together; HL = Hearing loss; Prim/sec = Primary/secondary school only; AC = Audiological centre; PT = physical therapy

Confirmatory Factor analysis

The adequacy of the 1-factor and 2-factor solutions was tested on the validation sample by performing Confirmatory Factor Analyses (CFA). Additionally, the 2-facor solution, previously reported in studies with chronic pain patients, was tested. The assumptions of multivariate normality and linearity were assessed and maximum likelihood was used to estimate all the models.

First, the 1-factor solution was investigated. The hypothesized model was considered a marginal fit X^2 (14, N = 302) = 65.98, $p < .001$, Comparative Fit Index (CFI) = .96. Considering the large sample the significant X^2 was expected. Post hoc model modifications were performed to develop a better fit resulting in a more parsimonious model. Figure 1 shows the hypothesized model where the circles represent the latent variables and the rectangles represent the measured variables. On the basis of the Lagrange Multiplier test ($p < .001$), three covariances were added to the model between the error terms corresponding to items 6 (*Self-care*) and 7 (*Life-support activity*), items 5 (*Sexual behaviour*) and 7 (*Life-support activity*), and items 3 (*Social activity*) and 4 (*Occupation*). Strong support was found for the final model X^2 (11, N = 302) = 16.96, p = .109, and a robust CFI = .995.

The same analyses were repeated in order to test the two-factor solution, found in the exploratory factor analysis in which a second factor was forced. Three covariances, based on the Lagrange Multiplier test ($p < .001$), were added between the error terms corresponding to items 5 (*sexual behaviour*) and 6 (*self-care*), items 4 (*Occupation*) and 7 (*life-support activity*), and items 3 (*Social activity*) and 4 (*Occupation*), which resulted in a more parsimonious model (see Figure 2). Again, strong support was found for this 2-factor solution, with slightly better indices on first sight, X^2 (10, N = 302) = 11.79, p = .299, and robust comparative fit index (CFI) = .998.

TABLE 3. FACTOR LOADINGS OF THE 1 FACTOR- AND 2 FACTOR SOLUTIONS FROM EXPLORATORY FACTOR ANALYSIS

		1 factor model	2 factor model	
Item	Content summary	Factor I	Factor I	Factor II
1	Family/home responsibilities	,83	,69	,21
2	Recreation	,82	,86	,05
3	Social Activity	,80	,95	-,12
4	Occupation	,80	,85	,04
5	Sexual behaviour	,77	,19	,63
6	Self care	,70	,34	,55
7	Life-support activity	,69	-,12	,97
	Percent of variance	60,13	62,13	10,49

A third analysis was carried out in which the 2-factor model, derived from previous psychometric research of the PDI (voluntary vs. obligatory activities) was tested. Post hoc model modifications were needed for a more parsimonious model and based on the Lagrange Multiplier test ($p < .001$) a total of 5 covariances were added. Figure 3 illustrates the final model with covariances between the error terms corresponding to items 5 (*sexual behaviour*) and 7 (*life-support activity*), items 3 (*Social activity*) and 4 (*Occupation*), 4 (*Occupation*) and 7 (*life-support activity*), items 2 (*recreation*) and 5 (*sexual behaviour*), and items 1(*family/home responsibilities*) and 3 (*Social activity*). Again, robust indices, X^2 (10, N = 302) = 11.79, p = .299, and a robust CFI = .999, were found for this solution.

Since all models resulted in robust fit indices, the root mean square error of approximation (RMSEA) with 90% confidence intervals, the Goodness of fit (GFI), and Adjusted goodness of fit (AGFI), the Akaike Information criterion (AIC), and the Consistent Akaike Information criterion (CAIC) were examined and evaluated against published guidelines (Bentler, 1990; Hu, Bentler, & Kano, 1992; Tabachnick & Fidell, 2007). For comparative purposes, indices for all three models are listed in Table 4. Robust goodness of fit was found for all three models; however, the CAIC indicates that the 1-factor solution, as was found initially in our EFA, might provide the best underlying structure of the TDI. Considering the principle of parsimony, and given the relatively high intercorrelation between both subscales, the 1-factor model was found to be most appropriate.

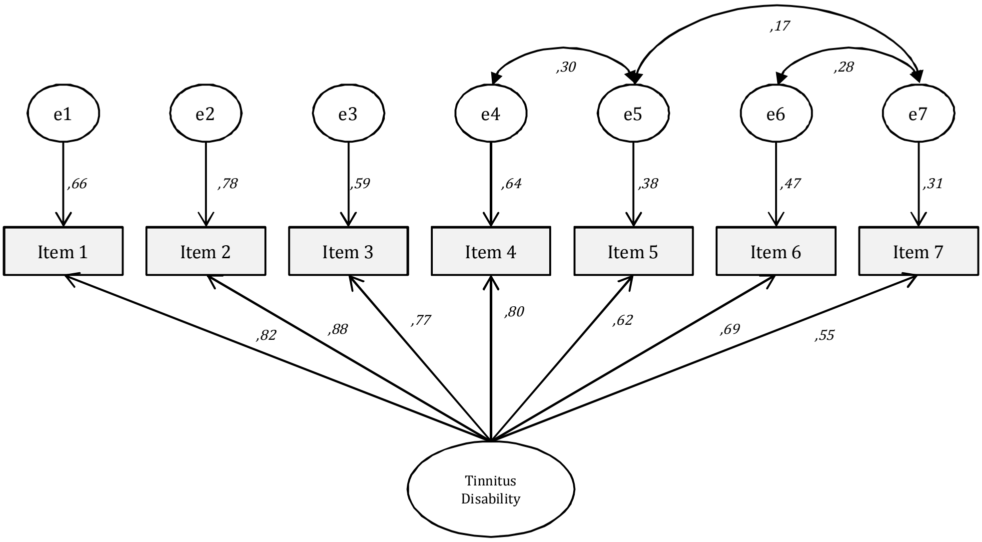

FIGURE 1. 1-FACTOR-MODEL WITH STANDARDIZED ESTIMATES AND ADDED CO-VARIANCES

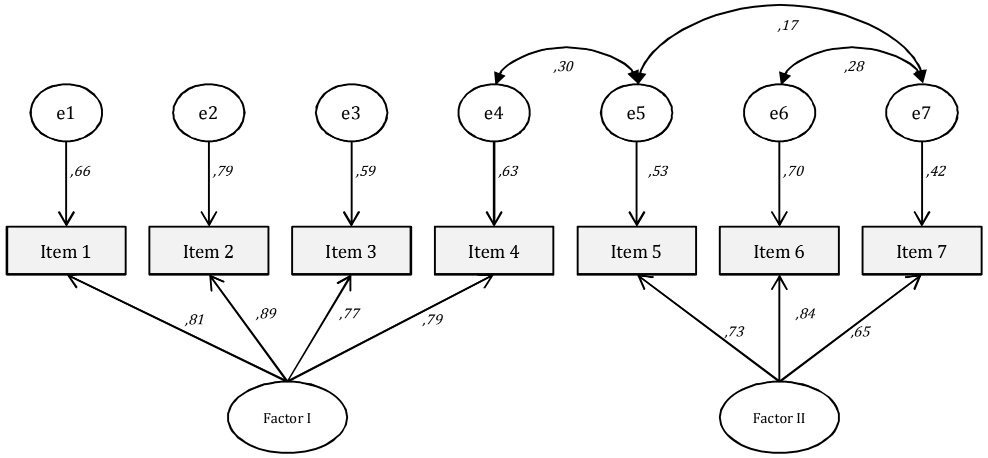

FIGURE 2. TWO-FACTOR-MODEL, FROM EXPLORATORY FACTOR ANALYSIS, WITH STANDARDIZED ESTIMATES AND ADDED COVARIANCES

Internal consistency

Reliability of the TDI was assessed on the whole sample and on the two subsamples separately. Internal consistency proved to be excellent, with Cronbach's alpha = .89 (total sample), Cronbach's alpha: .89 (calibration sample), and Cronbach's alpha: .90 (validation sample).

Reproducibility

Test-retest reliability was assessed by calculating an Intra-class Correlation Coefficient (ICC) between the test sample (first assessment = T0, *N=143*) and re-test sample (second assessment = T1, mean time interval of 4 weeks, *N=143*,), using a 2-way random effects model. Since tinnitus-related disability was expected to be a fairly stable construct, especially over this short period of time, the ICC of total TDI scores (*r=.76, p < .001)* points out good single measure test-retest reliability.

Construct validity

In order to investigate construct validity of the TDI associations between the TDI, Tinnitus Intensity, the SF36 and the TQ were investigated using a subset (N=385) of the total sample.

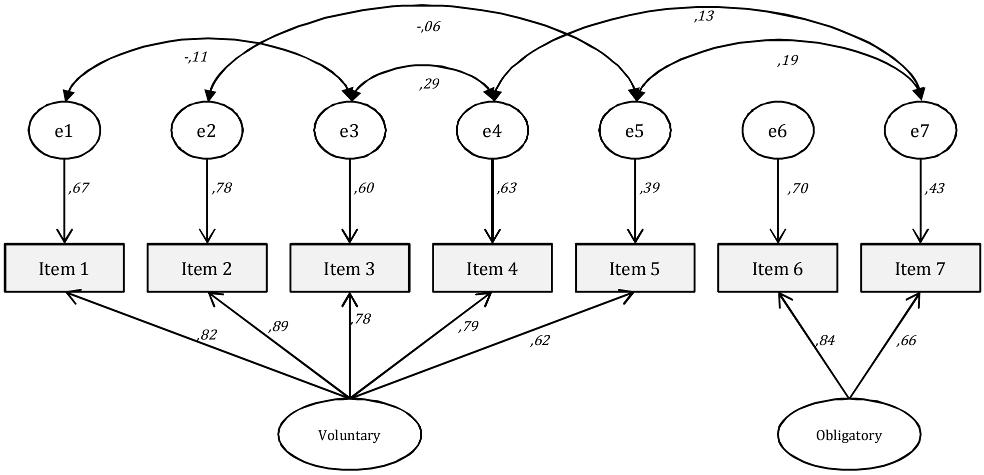

FIGURE 3. TWO-FACTOR SOLUTION, MODELED AFTER THE PAIN DISABILITY INDEX, WITH STANDARDIZED ESTIMATES AND ADDED COVARIANCES

TABLE 4. FIT INDICES OF THE 1-FACTOR AND BOTH 2-FACTOR SOLUTIONS WITH CONFIRMATORY FACTOR ANALYSIS

Model	X^2/ df	P	CFI	RMSEA	GFI	AGFI	AIC	CAIC
Model I:								
1-factor	*1.54*	*.109*	*.995*	*.042*	*.984*	*.960*	*50.96*	*131.04*
Model II:								
2-factor with 2nd factor pushed	*1.18*	*.299*	*.998*	*.024*	*.989*	*.969*	*47.79*	*132.58*
Model III:								
2-factor modelled after PDI (16)	*1.15*	*.328*	*.999*	*.022*	*.992*	*.970*	*49.78*	*143.39*

Correlations

Pearson correlation coefficients were calculated in order to test bivariate associations between all variables (see Table 5). As was expected, correlations between the TDI, Tinnitus Intensity, the SF36, and the TQ were moderate (ranging from .46 to .71), but statistically significant.

TABLE 5. MEANS, STANDARD DEVIATIONS, AND PEARSON CORRELATION COEFFICIENTS

	M	SD	TDI	Intensity	SF36	TQ
Intensity	*57,1*	*19,9*	0,48 (**)	-	0,29 (**)	0,59 (**)
SF36	*45*	*9,10*	0,46 (**)	0,29 (**)	-	0,44 (**)
TQ	*45,6*	*18,8*	0,71 (**)	0,59 (**)	0,44 (**)	-
Age	*53,5*	*11,2*	-0,07	0,04	-0,09 (*)	0,02
Duration	*5,4*	*1,50*	0,02	0,13 (*)	-0,05	0,02
Gender	-	-	-0,01	0,03	-0,01	-0,08
Education	-	-	-0,08	-0,19 (*)	-0,13 (**)	-0,25 (**)

* Correlation is significant at the 0.05 level (2-tailed)
** Correlation is significant at the 0.01 level (2-tailed)

TABLE 6. RESULTS OF HIERARCHICAL REGRESSION ANALYSIS WITH TINNITUS DISABILITY (TDI) AS DEPENDENT VARIABLE

IV	Step 1			Step 2			Step 3			Step 4		
	Stand. β	P	R²	Stand. β	P	R²	Stand. β	P	R²	Stand. β	P	R²
Age	-0,06	.24		-0,07	.11		-0,02	.58		-0,05	.17	
Gender	0,00	.98		-0,02	.67		-0,01	.83		0,08	.03	
Edu	-0,10	.07	0,01	-0,01	.91		0,03	.50		0,11	.03	
Intensity				0,49	.00	0,24*	0,39	.00		0,08	.08	
GH							0,34	.00	0,34*	0,17	.00	
Severity										0,64	.00	0,56*

IV = Independent Variables; Edu = Education; GH: General health
* Correlation is significant at the 0.01 level (2-tailed)

Regression Analyses

A stepwise hierarchical regression analysis was carried out in order to investigate which of the measures uniquely contributed to the variance in tinnitus disability, controlled for age, gender, and education. The first step in the analysis included the control variables age, gender, and education. This model yielded no significant F-value *(R^2=.01, F=1.44, P=.08).* Tinnitus Intensity and the SF36 were added in the step 2 and 3 of the hierarchical regression (see Table 5) and significantly contributed to total explained variance of Disability due to tinnitus *(R^2=.24, F=29.73, P=.00; R^2=.34, F=39.6, P=.00*). Last, the TQ was added. Results showed that tinnitus severity added significantly to the model with an extra 22% of explained variance *(R^2Change=.22, P<.001*). In the final step education reached significance (See Table 6) *(Total model: R^2=.56, F=81.3, P=.00).* There was no problem of multicollinearity between the independent variables (VIF's > 1.85).

Discussion

Although several measures exist that can be used to quantify the impact of tinnitus complaints on patients' cognitive, emotional, physical, and even auditory functioning, there currently is no measure available that specifically focuses on functional disability, that is, the interference of tinnitus with performance on major daily life activities. In the current study, a slightly adapted version of the PDI resulting in the TDI was administered to a large sample of individuals suffering from tinnitus. A first psychometric examination of this novel measure was carried out, including factor structure analysis, and the analysis of reliability and construct validity.

A principal component analysis on a random-split calibration sample generated a 1-factor solution accounting for 60% of explained variance. Since the TDI is a brief inventory this unitary solution was judged to be appropriate. This model was verified in a confirmatory factor analysis on the validation sample after 3 significant fit-modifications were applied. Consistent with earlier findings from Tait, Chibnall & Krause (Tait, et al., 1990) studying pain disability, as measured with the PDI, a second factor was forced using the calibration sample. The resulting 2-factor solution was currently found to account for over 72% of total variance. Interestingly, these findings did not corroborate PDI findings entirely. Although two internally consistent factors were generated, the factor loadings revealed different loadings of items on the factors than expected. Confirmatory factor analysis resulted in a robust and parsimonious 2-factor solution for this model and in order to investigate the comparative fit of the 2-factor solution proposed by Tait and others (Gauthier, et al., 2008; Tait & Chibnall, 2005; Tait, et al., 1990); this model was also investigated using confirmatory analysis. Again, fit indices revealed a robust and parsimonious model. However, reliability analysis showed that the 1 and 2 factor models currently investigated had internally consistent subscales ranging from good to excellent, whereas the obligatory subscale of the Tait model was not reliable.

Comparative fit indices showed that both 2-factor models did not have a better fit over the 1 factor solution, found initially in our calibration sample. This led to the conclusion that the 1-factor structure was most parsimonious and this unitary model was adopted. Corroborating these findings the test-retest reliability of the TDI as a 1-factor measure over a 4 week period proved to be satisfactory as well.

Robust evidence was found for construct validity of the TDI. Tinnitus related disability was expected to be associated with tinnitus intensity, ratings of general health and tinnitus severity. Pearson correlations among measures of tinnitus intensity, quality of life (SF36) and tinnitus distress (TQ) are relatively low, suggesting that disability as measured with the TDI is conceptually distinct from the other tinnitus related constructs, and that it seems to measure a unique underlying construct. Tinnitus intensity, as measured with 3 different Visual Analogue Scales was found to be significantly associated with ratings of tinnitus disability. Furthermore, general health significantly contributed to the model above and beyond tinnitus intensity, suggesting that participants with poorer general health reported more interference of the tinnitus in daily life activities. Tinnitus severity or distress due to tinnitus, finally, was an additional predictor of tinnitus related disability, again above and beyond tinnitus intensity, and general health. The relatively low betas suggest that other factors likely influence tinnitus disability, of which perceived threat value and tinnitus-related fear responses are good candidates. Indeed, the predictive value of these factors on disability have been well established in chronic pain research (Crombez, Vlaeyen, Heuts, & Lysens, 1999; Gheldof, et al., 2010; Jensen, Karpatschof, Labriola, & Albertsen, 2010; Leeuw, et al., 2007; Vlaeyen & Linton, 2000) and it would be interesting to investigate whether fear of tinnitus is as disabling as the tinnitus itself, or perhaps more so (Crombez, et al., 1999)

There are some limitations worth mentioning concerning the current investigation. *First*, these results concern cross-sectional data, and causality cannot be inferred from regression analyses. Experimental manipulations of the suggested predictors are needed in future research to scrutinize the causal pathways that lead to tinnitus disability. *Second*, audiometrical measurements, such as level and lateralization of hearing loss, tinnitus pitch match frequency, and maskability were not available and consequently were not taken into account in the current study. Future research investigating how audiometric data are associated with disability due to tinnitus in daily life is needed since earlier reports suggest that audiological dysfunctions like hearing loss and Hyperacusis are associated with tinnitus impairment (Andersson, 2003; Holgers, et al., 2005). *Third*, a self-selection bias may have occurred because of the web-based administration of the questionnaires in this study. Although participants were given the opportunity to complete the battery off-line as a classical paper-and-pencil test as well, the majority of respondents completed the measures online. It could be argued that individuals without computer skills, or not in possession of a PC, occur mainly in the older population, and might be under-represented in the current study. However, the mean age of participants does not seem to imply overrepresentation of younger respondents in the current study. *Fourth*, it should be noted that most respondents completed the online version of the TDI, and therefore we can conclude that the psychometric qualities of the electronic version of the TDI have been currently established. The web based nature of the current study is, on the other hand, in line with recent developments in research and the trend to offer online therapy and measurements (Abbott, et al., 2009; Andersson & Kaldo, 2004; Kaldo, et al., 2008). *Fifth*, it should be noted that the current investigation was carried out in a Dutch speaking population. The validity of the TDI in other languages still has to be established. *Finally*, correlations might be artificially increased due to shared method variance.

Results provide firm support that the TDI as a unitary brief index, is reliable over time, and is a valid measure for assessing tinnitus-related disability. When examining the 2-factor structure, the findings are not entirely synchronous with those in chronic pain patients. Even though parallels between chronic pain and chronic tinnitus have been described, differences may exist between the symptoms as well. In chronic pain patients, interference with voluntary and involuntary activities by pain might be different from the interference with these activities by tinnitus in tinnitus patients. Possibly this is due to the fact that physical movement is probably much more compromised in chronic pain as compared to tinnitus patients. Also, the behavioural responses to chronic pain and tinnitus are likely to be different. Future research should be aimed at investigating the nature of these behavioural responses in tinnitus patients and how they affect disability.

The TDI may constitute a valuable addition to the commendable tools already in use for several reasons. *First*, it is a brief and easily administered index. *Second*, it appears to capture a unique construct, namely tinnitus disability, or the experienced interference of the tinnitus with daily life activities, which is invaluable in the assessment and treatment of tinnitus patients. *Third*, medical insurance companies often times address issues like impact on daily living or impairment in daily life when investigating whether or not treatment is covered for a particular patient, which is imperative for treatment options for clinicians. *Fourth*, the TDI is notable for the limited confounding content overlap with other constructs, such as psychological distress, audiological impairment, or general health (Nicholls, Licht, & Pearl, 1982). Therefore, the TDI might be particularly useful in comparative effectiveness studies of existing and novel tinnitus-interventions, as well as in experimental research, aimed at disentangling the neuro-cognitive and behavioural mechanisms underlying tinnitus disability.

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Appendix A: Tinnitus Disability Index

The rating scales below are designed to measure the degree to which several aspects of your life are presently disrupted by the tinnitus. In other words, we would like to know how much the tinnitus is preventing you from doing what you normally do, or from doing it as well as you normally would. Respond to each category by indicating the overall impact of the tinnitus in your life, not just when the tinnitus is at its worst. For each of the 7 categories of life activity listed, please circle the number on the scale which describes the level of disability you typically experience. A score of 0 means no disability at all, and a score of 10 signifies that all of the activities in which you would normally be involved have been totally disrupted or prevented by your tinnitus.

1. Family/home responsibilities

This category refers to activities related to the home or family. It includes chores or duties performed around the house (e.g. yard work) and errands or favours for other family members (e.g. driving the children to school).

0 1 2 3 4 5 6 7 8 9 10

No disability Total disability

2. Recreation

This category includes hobbies, sports, and other similar leisure time activities.

0 1 2 3 4 5 6 7 8 9 10

No disability Total disability

3. Social activity

This category refers to activities which involve participation with friends and acquaintances other than family members. It includes parties, theatre, concerts, dining out, and other social functions.

0 1 2 3 4 5 6 7 8 9 10

No disability Total disability

4. Occupation

This category refers to activities that are part of or directly related to one's job. This includes non-paying jobs as well, such as that of a housewife or a volunteer worker.

0 1 2 3 4 5 6 7 8 9 10

No disability Total disability

5. Sexual behaviour

This category refers to the frequency and quality of one's sex life.

0 1 2 3 4 5 6 7 8 9 10

No disability Total disability

6. Self-care

This category includes activities which involve personal maintenance and independent daily living (e.g. taking a shower, driving, getting dressed, etc.).

0 1 2 3 4 5 6 7 8 9 10

No disability Total disability

7. Life-support activity

This category refers to basic life-supporting behaviours such as eating, sleeping and breathing.

0 1 2 3 4 5 6 7 8 9 10

No disability Total disability

CHAPTER IV

CATASTROPHIZING AND FEAR OF TINNITUS PREDICT QUALITY OF LIFE IN PATIENTS WITH CHRONIC TINNITUS

Based on

Cima, R. F. F., Crombez, G., & Vlaeyen, J. W. S. (2011). Catastrophizing and Fear of Tinnitus Predict Quality of Life in Patients With Chronic Tinnitus. Ear and Hearing, 32(5), 634-641

Abstract

Objectives: It is well established that catastrophic mis-interpretations and fear are involved in the suffering and disability of patients with chronic pain. This study investigated whether similar processes explain suffering and disability in patients with chronic tinnitus. We hypothesized that patients who catastrophically (mis)interpret their tinnitus would be more fearful of tinnitus, more vigilant towards their tinnitus, and report less quality of life. Moreover, tinnitus-related fear was expected to act as a mediator in reduced quality of life.

Design: Sixty-one tinnitus patients from an outpatient ENT department of the university hospital of Antwerp (Belgium) completed a number of questionnaires about their tinnitus. Hierarchical regression analyses were performed to test hypothesized associations and to assess mediation by tinnitus-related fear.

Results: Analyses revealed significant associations between catastrophizing and fear, and between catastrophizing and increased attention towards the tinnitus. Furthermore, both tinnitus-related catastrophizing and fear were negatively associated with quality of life and moreover, tinnitus-related fear fully mediated the association between catastrophizing about the tinnitus and quality of life.

Conclusions: The findings confirm earlier suggestions that tinnitus-related concerns and fears are associated with impaired quality of life, which is in line with a cognitive behavioural account of chronic tinnitus. Future research avenues and clinical applications are discussed.

Keywords: Catastrophizing; Cognitive-behavioural; Quality of life; Tinnitus; Tinnitus-related fear

Introduction

Tinnitus is the awareness of a sound without an external source. Several theories regarding its pathophysiology exist of which the most advocated is the hypothesis that tinnitus occurs as a result of spontaneous anomalous neural activity, coinciding with changes in the auditory system at any level along the auditory axis. Tinnitus has been described as a phantom auditory perception and the involvement of non-auditory structures are considered of key importance in clinically relevant tinnitus complaints (Cacace, 2003; Jastreboff, 1990; Jastreboff & Hazell, 1993).

The larger part of individuals experiencing chronic tinnitus eventually habituates or adapts to the tinnitus sound and is able to function fairly well. Only a small part (5–8 %) of this group tinnitus remains distressing and disabling (Ahmad & Seidman, 2004). In individuals with persistent tinnitus complaints, the acoustical characteristics of the tinnitus (e.g. loudness or pitch) are not univocally related to the severity of the tinnitus or treatment outcome (Jastreboff, 1990; Jastreboff & Hazell, 1993). Only a weak relationship can be established between perceived psycho-acoustic characteristics of the tinnitus (e.g. loudness or pitch) and the severity of complaints. In chronic tinnitus, the interpretation of the sound might be more important in defining the severity of complaints than the sound itself (Andersson, 2003; Henry & Meikle, 2000; Hiller & Goebel, 2007; Jastreboff & Hazell, 1993).

Severe emotional distress, major declines in concentration, problems in directing attention and sleeping difficulties are the most reported daily activity limitations caused by tinnitus. Most significant in predicting the variability in quality of life of tinnitus patients is psychological distress, including negative attitudes and cognitions, impaired concentration, insomnia, depression, and anxiety (Erlandsson & Hallberg, 2000). Accumulating evidence suggests that cognitive misinterpretations, negative emotional reactivity and attentional processes are crucial in dysfunctional habituation leading to severe tinnitus distress (Andersson & McKenna, 2006; Erlandsson & Hallberg, 2000; Kroner-Herwig, Frenzel, Fritsche, Schilkowsky, & Esser, 2003; Zachriat & Kroner-Herwig, 2004). In other chronic disorders, like irritable bowel syndrome (Gonsalkorale, 2004), chronic fatigue syndrome (Deary, Chalder, & Sharpe, 2007), and chronic pain disorder (Gatchel, Peng, Peters, Fuchs, & Turk, 2007), psychological mechanisms, predicting or promoting dysfunctional responses to symptoms, have similarly shown to be significant predictors of suffering (Crombez, Vlaeyen, Heuts, & Lysens, 1999; Rief & Broadbent, 2007).

Given the analogies between chronic tinnitus and chronic pain (Folmer, Griest, & Martin, 2001; Tonndorf, 1987), the current study is an attempt to apply a cognitive behavioural model of chronic musculoskeletal pain and disability to the problem of chronic tinnitus. The Fear-Avoidance (FA) model, originally proposed by Lethem et al. (Lethem, Slade, Troup, & Bentley, 1983) and further elaborated by Vlaeyen and Linton (Vlaeyen & Linton, 2000), is based on classical and operant conditioning paradigms. In case of injury, automatic emotional and sympathetic responses are elicited. Through classical conditioning a threatening situation, signalling pain or (re) injury, elicits conditioned fear responses such as increased arousal, hypervigilance, and avoidance and escape behaviours, negatively reinforced through instant diminishing fear. Although these protective behaviours may be adaptive in the acute phase, they maintain fear in the long run and lead to increased functional disability.

The FA model builds upon these principles and includes pain catastrophizing and pain-related fear as key factors. Pain catastrophizing can be defined as the process in which pain receives an extremely negative meaning, consisting of magnification of the stimulus, rumination about its possible consequences, and perceived helplessness and loss of control (Sullivan, Kues, & Mayhew, 1996). Pain related fear can be defined as the fearful reactions towards pain and pain-related activities and fear of (re)injury, including fearful beliefs about causes of pain. The FA model predicts that if pain is misinterpreted catastrophically, it will elicit specific pain-related fear associated with safety behaviours. These behaviours may be functional in the short-term as fear is decreased, but paradoxically they worsen the problem in the long run, because of disuse and increased disability.

The importance of pain-related fear in the development of pain-related disability has been previously established as being pivotal in the development of pain-related disability, contributing to disability more than biological or physical factors do (Crombez, et al., 1999; Gheldof, et al., 2006; Goubert, Crombez, & Van Damme, 2004). Especially, the mediating role of pain-related fear has been postulated, and in fact it has been found in earlier studies that pain-related fear mediates the association between catastrophizing about pain and functional disability (Gheldof, et al., 2006). The role of mediators in the maintenance of tinnitus distress has been proposed previously as well. Andersson and Westin (2008) theorized that conditioned responses, such as fear, are likely to act as mediators in the maintenance of chronic tinnitus distress.

Similar to chronic pain, catastrophic misinterpretations of tinnitus are likely to lead to tinnitus-related fear, which is likely to be associated with escape/avoidance behaviours and heightened awareness of the sound. Catastrophizing and tinnitus-related fear, may lead to increased attention towards the stimulus, at the cost of the necessary attention for daily activities, in turn leading to frequent interruptions of daily tasks, interference with daily functioning, and compromised quality of life. Additionally, tinnitus-related fear may have a mediating effect on the association between catastrophic misinterpretation of the tinnitus and general quality of life.

The present aim is to investigate the applicability of the FA model in patients with chronic tinnitus in a cross-sectional study. We hypothesized that patients who catastrophically misinterpret their tinnitus would be more fearful of tinnitus, and that both catastrophic misinterpretations and heightened fear are associated with increased attention towards the tinnitus. We also expected a strong inverse association between tinnitus-related catastrophizing and fear, and quality of life, moreover tinnitus-related fear was expected to mediate the effect of catastrophic misinterpretations on quality of life.

Materials and Methods

Participants

Sixty-one (mean age = 55.4 yrs, SD = 12.1) participants suffering from chronic tinnitus were recruited from an outpatient ENT department (See table 1 for demographic data). From all incoming ENT patients only those were included who reported to be mainly troubled by their tinnitus. Thirteen participants experienced difficulties in balance and dizziness secondary to their tinnitus, 4 subjects reported to be also incapacitated by their hearing loss and 1 reported to be troubled by hyperacusis next to the tinnitus. Duration of tinnitus was on average 2.6 years (SD=.9).

TABLE 1. DEMOGRAPHIC DATA: AGE, GENDER, DURATION AND EDUCATION

Age (yrs)	%	Duration (yrs)	%
< 35	5	< 1	4
35 < 50	33	1 < 5	21
50 < 65	33	5 < 10	15
65 <	28	10 <	60
Gender	**%**	**Education**	**%**
Male	40	Elementary	13
Female	60	Junior high	20
		High school	16
		College/university degree	51

Procedure

Research instruments were administered in an outpatient ENT department of the university hospital of Antwerp (Belgium) during a period of 6 months. The battery of instruments was administered after the purpose of the study was explained to participants and informed consent was obtained. The research protocol was approved by the ethical board of the faculty of Psychology and Educational Sciences of the Ghent University in Belgium.

Measures

Distress caused by the tinnitus or tinnitus severity was assessed by the Tinnitus Questionnaire (TQ). The TQ consists of 52 items rated on a 3-point scale and assesses the psychological distress associated with the tinnitus. Psychometric properties of the TQ have proven excellent in different languages (Baguley, Humphriss, & Hodgson, 2000; McCombe, et al., 2001).

General distress was measured with the Hospital Anxiety and Depression Scale (HADS), which was successfully used in tinnitus research previously (Andersson, 2002). The Dutch version of the HADS contains 14 items and has good reliability and validity (Spinhoven, et al., 1997).

Tinnitus severity and general distress were assessed for descriptive purposes. The following measures were used to assess Quality of life, Catastrophizing about tinnitus, Tinnitus-related fear, and attention towards the tinnitus.

Quality of life was assessed by the Short Form – 36 (SF36) (Hays, Sherbourne, & Mazel, 1993) which comprises 36 items to assess various aspects of quality of life, including physical functioning, bodily pain, emotional functioning, mental health, vitality and social functioning. Two general subscales can be calculated: physical and mental health. In the current study the mean of both scores has been used as a single measure for overall health (El Refaie, et al., 2004).

Catastrophizing about tinnitus was measured by the Tinnitus Catastrophizing Scale (TCS). The TCS (see appendix 1) is an adapted version of the Pain Catastrophizing Scale (Sullivan, et al., 1996; Van Damme, Crombez, Bijttebier, Goubert, & Van Houdenhove, 2002). The word 'pain' was substituted by the word 'tinnitus'. The TCS has13 items to be rated on a 5-point scale (0 = not at all, 4 = always).

Tinnitus-related fear was assessed with the Fear of Tinnitus Questionnaire (FTQ). Of this novel measure, items were included that were believed to capture worries and fears of patients experiencing tinnitus (see appendix 2). Some of the FTQ items were derived from the Tampa scale for Kinesiophobia (Roelofs, et al., 2007) and the Pain Anxiety Symptoms Scale (McCracken, Zayfert, & Gross, 1992). The FTQ was pretested with patients. The FTQ has 17 items to be rated on a true or false scale.

Attention towards the tinnitus was measured by the Tinnitus Vigilance and Awareness Questionnaire (TVAQ). This novel 18-item measure (see appendix 3) is based on the 16-item Pain Vigilance and Awareness Questionnaire (PVAQ) (Roelofs, Peters, McCracken, & Vlaeyen, 2003). Items 2, 3, 4, 6, 7, 8, 9, 10, 13 and 14 are PVAQ items, in which the word 'pain' was substituted by the word "tinnitus". The remaining items that were included were believed to capture heightened awareness of tinnitus. Items are to be rated on a 6-point scale (0 = never, 5 = always).

Statistical procedures

First, for all tinnitus self-report measures and the quality of life measure, Cronbach's Alpha was calculated in order to test internal consistency. Second, Pearson correlation coefficients were calculated in order to test bivariate associations between measures. Third, a series of multiple hierarchical regression analyses was carried out to test the hypotheses that [1] catastrophizing about tinnitus is associated with fearful responses, [2] both catastrophizing about tinnitus and tinnitus-related fear are associated with increased attention towards tinnitus, and that [3] both predict poorer quality of life. Additionally, [4] to test for mediation of tinnitus-related fear on the association between tinnitus catastrophizing and general quality of life the asymptotic and re-sampling procedure for estimating the indirect effects proposed by Preacher and Hayes (Preacher & Hayes, 2004, 2008) was chosen since this approach has more power over the more frequently used method proposed by Baron and Kenny, which includes the Sobel-test to test for mediation (Baron & Kenny, 1986). Moreover, this procedure provides a quantified estimate of the indirect effect with associated confidence limits. Predicted associations are illustrated in figure 1. In all regressions analyses, as well as in the re-sampling procedure to test for mediation, age, gender, and education level were entered as co-variables. For all statistical procedures SPSS version 18.0 for Windows was used.

Results

Descriptive data

Patients reported a mean TQ-score (tinnitus distress) of 50 (SD=16.8) indicating that on average severe distress associated with tinnitus was experienced (TQ- cut off = 46). In line with suggestions from McCombe et al. (McCombe, et al., 2001) we further classified patients in terms of their TQ-scores. Scores on the TQ and location of the tinnitus in the current sample are depicted in figure 2.

Mean scores on the HADS depression and anxiety subscales were 6.4 (SD=4.5) and 7.6 (SD=4.6) respectively. Scores below 8 indicate that pathological anxiety or depression is absent (Spinhoven, et al., 1997). On the depression subscale, 43.3% of respondents scored above this clinical cut-off score. On the anxiety subscale this was 48.3% of respondents. No significant differences were found between male and female patients in age, tinnitus severity, or depressive or anxious mood.

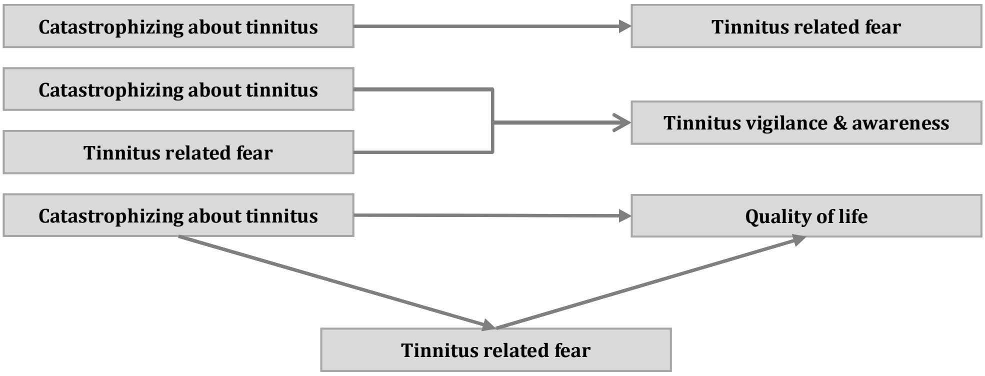
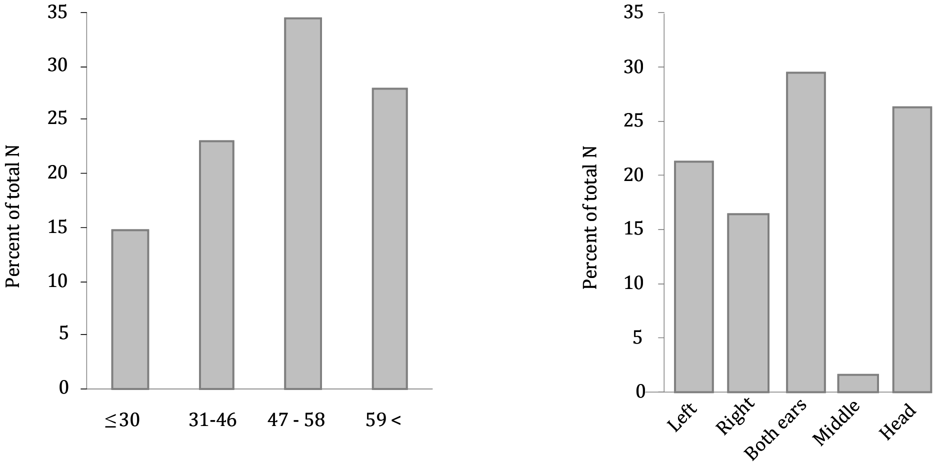


Figure 1. Predicted associations between catastrophizing about tinnitus (TCS), tinnitus-related fear (FTQ), increased attention towards tinnitus (TVAQ) and quality of life (SF36)



2a) TQ scores

2b) Tinnitus location

Figure 2. (a) Scores on the Tinnitus Questionnaire (TQ) and (b) tinnitus location

The internal consistency (Cronbach's α) of all self-report measures were excellent (TCS, α= .93, FTQ, α= .82, TVAQ, α= .81, and SF36, α= .93, TQ= .90, HADS Depression and Anxiety, α= .86 and α= .85 respectively).

Correlations

Table 2 displays means, standard deviations and Pearson correlations among the TQ, TCS, the FTQ, the TVAQ, the SF36 and age. Correlations between TQ, TCS, FTQ, TVAQ, SF36 on the one hand and age on the other hand were not significant. As was expected, correlations among the tinnitus scales were significantly positive. The significant correlations between the TQ and the TCS, FTQ, and the TVAQ support the convergent validity of these new scales. Significant negative correlations were found between quality of life and distress due to tinnitus, catastrophizing about tinnitus, tinnitus-related fear, and increased attention towards tinnitus, supporting the divergent validity.

TABLE 2. MEANS, STANDARD DEVIATIONS, AND PEARSON CORRELATION COEFFICIENTS

Variabels	Mean	SD	2	3	4	5	6
Tinnitus severity (TQ)	15	16.8	.74**	.70**	.57**	-.57**	-.01
Tinnitus Catastrophizing (TCS)	25.1	13.7	-	.70**	.62**	-.32*	.05
Fear of tinnitus (FTQ)	43.6	8.2	-	-	.42**	-.43**	.13
Increase attention towards the tinnitus (TVAQ)	49.6	15.4	-	-	-	-.31*	-.08
Quality of life (SF36)	53.3	8.4	-	-	-	-	-.03
Age	55.71	11.93	-	-	-	-	-

Note: *P < .05 (2-tailed); **P < .01 (2-tailed). TQ: Tinnitus questionnaire; TCS: Tinnitus catastrophizing scale; FTQ: Fear of tinnitus questionnaire; TVAQ: Tinnitus vigilance and awareness questionnaire; SF36: Short form 36

Regression analyses

CATASTROPHIZING ABOUT TINNITUS IS ASSOCIATED WITH TINNITUS-RELATED FEAR

In order to investigate whether the level of catastrophizing (TCS) contributes to tinnitus related fear (FTQ), a hierarchical regression analysis was performed. The first step in the analysis included the control variables age, gender, and education. This model yielded no significant F-value. Catastrophizing was added in the next step (see table 3) and significantly contributed to total explained variance of tinnitus related fear. The control variables did not reach significance. See table 3 for statistics from regression equations.

CATASTROPHIZING ABOUT TINNITUS AND TINNITUS-RELATED FEAR ARE ASSOCIATED WITH INCREASED ATTENTION TOWARDS THE TINNITUS

To assess whether catastrophic interpretations (TCS) of tinnitus are associated with increased attention towards the tinnitus (TVAQ), a second regression analysis was performed. Again demographic variables were entered first (age, gender, and education). This model did not reach significance. Adding catastrophizing in the next step yielded a significant model (see table 4; model 2 a).

TABLE 3. STATISTICS FROM REGRESSION EQUATIONS: TINNITUS CATASTROPHIZING (TCS) AS INDEPENDENT VARIABLE AND TINNITUS-RELATED FEAR (FTQ) AS DEPENDENT VARIABLE

Model	R2 change(F)	Independents	B		Stand B	
1	0.04(0.77)	Age	0.08		0.11	
		Gender	-1.92		-0.11	
		Education	-0.62		-0.08	
2	0.48(15.07)	Tinnitus Catastrophizing (TCS)	0.45	**	0.71	**

Note: *P < .05 (2-tailed); **P < .01 (2-tailed). TCS: Tinnitus catastrophizing scale; FTQ: Fear of tinnitus questionnaire

Next, catastrophizing about tinnitus was replaced by tinnitus-related fear to assess whether heightened fear is a predictor for increased awareness towards the tinnitus. Results show that in this case fear of the tinnitus added significantly to the model, controlled for age, gender, and education (See table 4; model 2 b).

A final analysis was performed to test whether heightened fear is related to increased attention towards the tinnitus, above and beyond catastrophizing about tinnitus. After controlling for age, gender and education, catastrophizing was added to the model first, and tinnitus-related fear was added last; results show that fear of the tinnitus no longer significantly added to the model (see table 4 for statistics from regression equations).

TABLE 4. STATISTICS FROM REGRESSION EQUATIONS: TINNITUS CATASTROPHIZING (TCS) AND TINNITUS-RELATED FEAR (FTQ) AS INDEPENDENTS AND INCREASED ATTENTION TOWARDS TINNITUS (TVAQ) AS DEPENDENT VARIABLE

Model	R2 change (F)	Independents	B		Stand B	
1	0.062(1.23)	Age	0.01		0.00	
		Gender	-0.22		-0.01	
		Education	3.37		0.25	
2 a	0.37(10.54)	Tinnitus Catastrophizing (TCS)	0.70	**	0.62	**
2 b	0.22 (16.50)	Fear of tinnitus (FTQ)	0.84	**	0.48	**
3	0.02(8.35)	Tinnitus Catastrophizing (TCS)	0.65	**	0.57	**
		Fear of tinnitus (FTQ)	0.12		0.07	

Note: *P < .05 (2-tailed); **P < .01 (2-tailed). TCS: Tinnitus catastrophizing scale; FTQ: Fear of tinnitus questionnaire; TVAQ: Tinnitus vigilance and awareness questionnaire

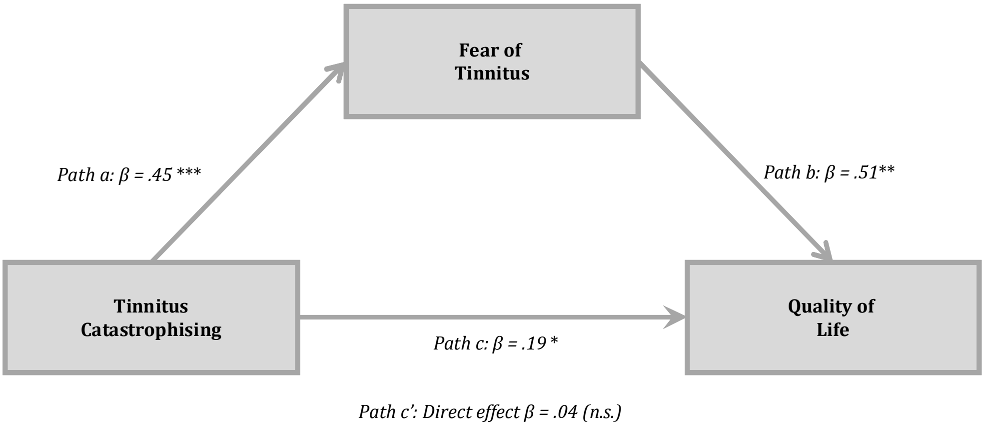
TABLE 5. STATISTICS FROM REGRESSION EQUATIONS: TINNITUS CATASTROPHIZING (TCS) AND TINNITUS-RELATED FEAR (FTQ) AS INDEPENDENTS AND QUALITY OF LIFE (SF36) AS DEPENDENT VARIABLE

Model	R2 change (F)	Independents	B		Stand B	
1	0.05(0.88)	Age	-0.08		-0.10	
		Gender	1.89		0.11	
		Education	-1.73		-0.22	
2	0.08(1.97)	Tinnitus Catastrophizing (TCS)	-0.19	**	-0.29	**
3	0.12(3.46)	Tinnitus Catastrophizing (TCS)	0.04		0.06	
		Fear of tinnitus (FTQ)	-0.51	**	-0.50	**

Note: *P < .05 (2-tailed); **P < .01 (2-tailed)
TCS: Tinnitus catastrophizing scale; FTQ: Fear of tinnitus questionnaire; SF36: Short form 36

CATASTROPHIZING ABOUT TINNITUS AND TINNITUS-RELATED FEAR ARE ASSOCIATED WITH QUALITY OF LIFE

A final hierarchical regression analysis was performed to assess whether the level of catastrophizing (TCS) and tinnitus-related fear (FTQ) would both have a unique contribution in explaining poorer quality of life (SF36). The first step in the model included age, gender, and education, none of which reached significance (see table 5). Adding the level of catastrophizing contributed significantly to the model. Adding heightened fearfulness of the tinnitus in the third step again yielded significant results. See table 5 for statistics from regression equations.



Note: *P < .05 (2-tailed); **P < .01 (2-tailed); * * * P < .001

FIGURE 3. THE MEDIATOR MODEL WITH TINNITUS RELATED FEAR (FTQ) AS THE MEDIATOR IN THE ASSOCIATION BETWEEN CATASTROPHIZING ABOUT TINNITUS (TCS) AND QUALITY OF LIFE (SF36). STANDARDIZED BETA'S OF INDIVIDUAL PATHS, AND THE STANDARDIZED BETA OF THE DIRECT EFFECT.

FEAR OF TINNITUS MEDIATES THE ASSOCIATION BETWEEN CATASTROPHIZING AND QUALITY OF LIFE

In order to assess mediation, the 'asymptotic and re-sampling' procedure for estimating the bias corrected indirect effects (Preacher & Hayes, 2004, 2008) was chosen. Both test statistics and the confidence interval of the indirect effects indicate a full mediating effect of tinnitus related fear on the association between tinnitus catastrophizing and quality of life (see figure 3 for the mediator model and statistics). In table 6 the coefficients and test statistics of the control variables (age, gender and education) and the mediation paths (see figure 3) are listed and in table 7 the confidence intervals of the indirect effect after re-sampling are listed.

TABLE 6. PARTIAL EFFECT OF CONTROL VARIABLES ON DEPENDENT VARIABLES AND INDIRECT, TOTAL AND DIRECT EFFECTS OF THE MEDIATION MODEL

Control variables	Effects	Coefficients	Standard error	p	
Age		-.04	.09	.66	
Gender		1.08	2.20	.62	
Education		-2.12	-2.02	.05	
	Path a	.45	.06	.00	*
	Path b	-.51	.18	.00	*
	Path c	-.19	.08	.02	*
	Path c’	.04	.11	.72	

Note: a path, effect of tinnitus catastrophizing on tinnitus related fear; b path effect of tinnitus related fear on quality of life, controlled for catastrophizing; c path, total affect, of tinnitus catastrophizing on quality of life (*significant effect see also figure 3); c’path, direct affect, of tinnitus catastrophizing on quality of life controlled for the mediator, all path analyses controlled for age, gender and education.

TABLE 7. MEDIATION OF THE EFFECT OF TINNITUS CATASTROPHIZING ON QUALITY OF LIFE THROUGH TINNITUS RELATED FEAR

Bootstrapping	Percentile 95% CI		BC 95% CI		Bca 95% CI	
	Lower	Upper	Lower	Upper	Lower	Upper
FTQ	-.3868	-.0690	-.4165	-.0662	-.4047	-.0710

Note: FTQ, Tinnitus related fear, BC, bias corrected; Bca bias corrected and accelerated;
2000 bootstrap samples, analyses controlled for age, gender and education

Discussion

The current study investigated whether catastrophic misinterpretations of tinnitus and tinnitus-specific fear would be important in explaining chronic tinnitus suffering and quality of life. A novel framework explaining chronic tinnitus complaints was presented; the fear-avoidance model of pain served as a heuristic framework to formulate specific hypotheses. Previous findings in tinnitus research corroborate the possible applicability of the FA model for chronic tinnitus. The importance of classical and operant learning principles in the maintenance and possible treatment avenues in chronic tinnitus complaints have been postulated before (Wilson, 2006). One of the assumptions of the neurophysiological model of tinnitus (Jastreboff, 1990; Jastreboff & Hazell, 1993; Jastreboff & Hazell, 2004) is that conditioned reflexes in processing the tinnitus sound are especially important in the development, habituation processes and recovery of disabling tinnitus. The neurophysiological model also postulates that in the generation and maintenance of chronic bothersome tinnitus, the perception and interpretation of the signal is strongly related to heightened negative emotional states, eliciting increased attention towards the tinnitus, enhancing the perception itself (Jastreboff, 1990). This is in accordance with the currently proposed FA model, which expands on these notions and incorporates a possible cognitive- behavioural account for the onset and maintenance of chronic bothersome tinnitus. Our findings support both models, in that they postulate the importance of the relation between interpretation of the signal and heightened negative emotional responses, with increased attention towards the signal and enhanced perception as a result.

Catastrophic misinterpretation was expected to influence the fearful response to the tinnitus sound. Furthermore, catastrophic misinterpretations of tinnitus and tinnitus-related fear were expected to be associated with a higher tendency to attend to the tinnitus. Last, we predicted that both catastrophizing about the tinnitus and a higher level of fear of tinnitus would be associated with lower quality of life and that tinnitus-related fear mediated the association between tinnitus catastrophizing and quality of life.

The current findings corroborate the parallels between chronic pain and chronic tinnitus. They suggest that the fear-avoidance model proposed in chronic pain literature extends to patients with chronic tinnitus. Almost all of the associations mentioned earlier were found to be significant. The level of catastrophizing was highly associated with both self-reported tinnitus specific fear and increased attention towards the tinnitus. Higher levels of tinnitus-related fear were associated with increased attention towards the tinnitus as well. However, this association was no longer significant after controlling for catastrophizing first. This might be due to the large conceptual overlap between catastrophizing about tinnitus and fearful reactions towards the tinnitus. Indeed, catastrophizing beliefs may be considered part of the overall fear construct, next to protective behaviours and physiological arousal (Lang, Levin, Miller, & Kozak, 1983). Finally, catastrophic misinterpretations of tinnitus were significantly related to poorer quality of life ratings and heightened fear uniquely added to this model, above and beyond the contribution of catastrophizing about tinnitus. Moreover, tinnitus-related fear fully mediated the association between tinnitus catastrophizing and quality of life.

Chronic tinnitus complaints are considered complex and difficult to treat or alleviate. It has not been possible to explain daily interference and disability caused by the tinnitus by the characteristics of the sound itself. Tinnitus sufferers report experiencing difficulties in concentration because of the tinnitus, and terms like “intrusiveness of the sound” distinguishes moderate from severe tinnitus in most subjective reports (Andersson & McKenna, 2006). Many theorists have proposed that psychological factors are the main predictors concerning tinnitus severity (Andersson, 2002; Hallam, McKenna, & Shurlock, 2004; Jensen, Turner, Romano, & Karoly, 1991). Moreover, cognitive behavioural therapy has been proven effective in several clinical trials (Andersson, 2002; Dobie, 1999; Kroner-Herwig, et al., 2003; Martinez Devesa, Waddell, Perera, & Theodoulou, 2007; Rief, Weise, Kley, & Martin, 2005). Tinnitus complaints might be best explained by adopting a biopsychosocial approach and using a cognitive behavioural framework. The cognitive tinnitus sensitization model proposed by Zenner and Zalaman (Zenner & Zalaman, 2004) introduced an explanation for the significant improvements in tinnitus complaints by cognitive behavioural therapy. Processes of inadequate appraisal, inadequate coping, negative affect, and increased attention towards the tinnitus were distinguished; however, the associations between these processes were not yet specified in a single theoretical framework. The current study is a first step in this direction. Our results are in accordance with previous findings in studies on chronic tinnitus and chronic pain, and seem to support a similar underlying cognitive behavioural model as the one proposed by Vlaeyen & Linton (2000). These findings provide important new insights regarding the role of cognitive misinterpretations and fear in the maintenance of chronic tinnitus. In fact, they suggest that catastrophic misinterpretation of tinnitus is not only highly associated with heightened fear of the tinnitus sound, but also with increased attention towards the threatening sound and lower ratings of quality of life. Moreover, findings suggest that tinnitus-related fear is associated with increased attention towards the tinnitus and with a decrease in quality of life as well. Interestingly, it was found that tinnitus specific fear fully mediated the relation between catastrophizing about tinnitus and quality of life. This finding suggests that tinnitus-related fear accounts for the relation between catastrophic misinterpretations of tinnitus and quality of life ratings.

In chronic pain research, the mediating role of fearful reactions has been investigated and established (Gheldof, et al., 2006; Goubert, et al., 2004). It was found that in the association between pain severity and functional and social disability, fear of painful movement had an important mediating effect. The theoretical concept of mediators in the maintenance of tinnitus distress has been previously proposed (Andersson & Westin, 2008). First it was brought to attention that the tinnitus receives its negative connotation through classical conditioning (Jastreboff & Jastreboff, 2006). It was furthermore theorized that aversive responses towards the tinnitus sound might act as mediators and be the prime cause of maintained tinnitus distress in the long run. The current findings corroborate these assumptions in that aversive responses, like catastrophizing and fear might be the key factors in the maintenance of chronic tinnitus distress with an important mediating role of tinnitus specific fear in this process.

This study has a number of limitations. *First,* it is important to note that the current investigation was carried out using measures initially developed for chronic pain research. Correlations between the TQ and the new measures were significant; indicating a high convergent validity. Divergent validity was indicated by the significant negative correlation between the SF36 and the tinnitus measures. Future research is needed to examine the psychometric properties of these instruments in larger samples of patients with tinnitus. *Second*, for reasons described below we used results on the TQ for descriptive purposes only. Guidelines for the grading of tinnitus severity have been described by Mc Combe et al. (McCombe, et al., 2001). They concluded that the grading of tinnitus severity is almost synonymous with grading psychological distress. Since tinnitus severity is largely determined by psychological factors, the instruments developed for this purpose, like the TQ, comprise items which are quite similar to those of more specific measures to assess level of catastrophizing, hypervigilance and tinnitus related fear. For this reason it was considered inappropriate in the current investigation to use the TQ as a reference for disability caused by the tinnitus or tinnitus severity, since this would compromise analyses. Severity of tinnitus should be otherwise specified when used for researching cognitive models, possibly within the realm of a biopsychosocial framework. Another option would be to include Visual Analogue Scales (VAS) in the future to establish tinnitus severity or impact on daily life. *Third*, these results concern cross-sectional data. Therefore, causality cannot be inferred from current data. *Fourth*, another risk worth mentioning is that shared method variance might be causing an artificial inflation of correlations in the current analyses (Nicholls, Licht, & Pearl, 1982). *Last*, audiological measurements, such as level and lateralisation of hearing loss, tinnitus localisation and pitch match frequency and intensity, maskability, and uncomfortable loudness levels (UCL) to assess for decreased sound tolerance were not available for analyses. In future studies it would be of interest to see whether these measures could predict interpretation, fear and attentional bias towards the tinnitus. It might also be important to investigate whether these psychological mechanisms affect tinnitus measures like maskability or subjective loudness (intensity) and sound tolerance.

In sum, the present study indicates important parallels between chronic pain and chronic subjective tinnitus. Important new insights regarding the role of cognitive misinterpretations and fear in the maintenance of chronic tinnitus and the mediating role of these fearful reactions towards the tinnitus have been presented. Important to note is that next to several parallels there are differences as well between chronic tinnitus and chronic pain disorder. For example, ineffective safety behaviours are assumed to play an important role in the maintenance of chronic tinnitus complaints. These safety behaviours are expected to be different from those observed in chronic pain patients, research efforts should be undertaken to further investigate the exact nature, occurrence, and consequences of these safety behaviours in tinnitus patients.

Results show that adopting a biopsychosocial approach, in studying development, maintenance, assessment and treatment approaches in chronic tinnitus might offer new venues for research and management of chronic tinnitus (Martinez Devesa, et al., 2007). Future efforts should focus on development and validation of appropriate measures, experimental studies in which value of tinnitus sounds are manipulated, and replication of results using larger samples employing a longitudinal design.

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Tinnitus Catastrophizing Scale (TCS)

We are interested in your thoughts en feelings when experiencing tinnitus. With this questionnaire we want to investigate what influence tinnitus has on you; on your mood, your behaviour, your attitude. Below you can find 13 statements describing different thoughts and feelings which might be related to your tinnitus. Please try to indicate to what extent these thought or feelings apply to you by using the following rating scale: *0 = Not at all; 1 = to a small extent; 2 = to some extent; 3 = to a large extent; 4 = Always*

If I experience Tinnitus ...

… I worry all the time about whether the tinnitus will end	☐
… I feel I can’t go on	☐
… It’s terrible and I think it’s never going to get any better	☐
… It’s awful and I feel it overwhelms me	☐
… I feel I can’t stand it anymore	☐
… I become afraid the tinnitus will get worse	☐
… I keep thinking about other times I experienced tinnitus	☐
…I anxiously want the tinnitus to go away	☐
… I can’t seem to keep it out of my mind	☐
… I keep thinking about how strong my tinnitus is	☐
… I keep thinking about how badly I want the tinnitus to stop	☐
… There is nothing I can do to reduce the intensity of the tinnitus	☐
… I wonder whether something serious may happen	☐

Appendix 2

Fear of Tinnitus Questionnaire (FTQ)

This questionnaire will help us understand how you think and feel about your tinnitus condition. It enables us to examine how tinnitus affects you, what effect is has on your mood, your behaviour, your attitude. Below you will find 17 statements. Please check the box next to each statement that you think applies to your current situation.

☐ 1 I am afraid that my tinnitus will deteriorate my hearing
☐ 2 I am afraid that my tinnitus will become worse
☐ 3 I fear that my tinnitus is the result of a tumour
☐ 4 Even though my tinnitus is getting worse, I do not think it points to a serious disease
☐ 5 I am afraid that my tinnitus will drive me crazy
☐ 6 The fact that I have tinnitus does not mean that my health is at risk
☐ 7 I am afraid my tinnitus will leave me deaf
☐ 8 I am afraid the moment will come that my head cannot withstand tinnitus anymore
☐ 9 My mental condition will become severely affected by my tinnitus
☐ 10 I am afraid that tinnitus will stop me from ever having a normal life again
☐ 11 I am afraid that I will never be able to experience silence again because of tinnitus
☐ 12 I am afraid that loud noises will aggravate my tinnitus
☐ 13 I am afraid I will not be able to do anything anymore because of my tinnitus
☐ 14 It worries me to think I may never be able to learn how to cope with this condition
☐ 15 It would be terrible if my tinnitus proved a life-long condition
☐ 16 I am concerned that tinnitus may be a risk to my physical health
☐ 17 I am afraid that tinnitus may be a preliminary sign of brain haemorrhage or similar

Appendix 3

Tinnitus Vigilance and Awareness Questionnaire (TVAQ)

Below you find 18 sentences describing how people react on their tinnitus. . With this questionnaire we want to investigate what influence tinnitus has on you; on your mood, your behaviour, your attitude. Please indicate how often a statement applies to you by circling a number between 0 (never) and 5 (always).

		Never		**Always**			
1	I am very aware of changes in my tinnitus	0	1	2	3	4	5
2	I am quick to notice changes in the intensity of my tinnitus	0	1	2	3	4	5
3	I am quick to notice the effects of medication on my tinnitus	0	1	2	3	4	5
4	I am quick to notice changes in sound or intensity of my tinnitus	0	1	2	3	4	5
5	The tinnitus keeps me constantly occupied	0	1	2	3	4	5
6	I notice the tinnitus even if I am busy with another activity	0	1	2	3	4	5
7	I find it easy to ignore my tinnitus	0	1	2	3	4	5
8	I know immediately when my tinnitus starts or increases	0	1	2	3	4	5
9	When I do something that increases my tinnitus, the first thing I do is check to see how much my tinnitus was	0	1	2	3	4	5
10	I know immediately when my tinnitus decreases	0	1	2	3	4	5
11	I must attend to my tinnitus a lot	0	1	2	3	4	5
12	I carefully monitor how intense my tinnitus is	0	1	2	3	4	5
13	I become preoccupied with my tinnitus	0	1	2	3	4	5
14	I do not dwell on my tinnitus	0	1	2	3	4	5
15	Sometimes I'm able to ignore the tinnitus, even if it is present	0	1	2	3	4	5
16	I am aware of my tinnitus from the moment I get up till the moment I go to sleep	0	1	2	3	4	5
17	The tinnitus distracts me, no matter what I do	0	1	2	3	4	5
18	Often, my tinnitus is so bad that I cannot ignore it	0	1	2	3	4	5

CHAPTER V

A STUDY PROTOCOL

COST-EFFECTIVENESS OF MULTIDISCIPLINARY MANAGEMENT OF TINNITUS AT A SPECIALIZED TINNITUS CENTRE

Based on

Cima, R. F. F., Joore, M.A., Maes, I.H., Scheyen, D.J.W.M., El Refaie, A., Baguley, D.M., Anteunis, L.J.C., Vlaeyen, J.W.S. (2009). Cost-effectiveness of multidisciplinary management of Tinnitus at a specialized Tinnitus centre. *BMC Health Services Research, 9*, 29.

Abstract

Background: Tinnitus is a common chronic health condition that affects 10% to 20% of the general population. Among severe sufferers it causes disability in various areas. As a result of the tinnitus, quality of life is often impaired. At present there is no cure or uniformly effective treatment, leading to fragmentized and costly tinnitus care. Evidence suggests that a comprehensive multidisciplinary approach in treating tinnitus is effective. The main objective of this study is to examine the effectiveness, costs, and cost-effectiveness of a comprehensive treatment provided by a specialized tinnitus center versus usual care. This paper describes the study protocol.

Methods/Design: In a randomized controlled clinical trial 198 tinnitus patients will be randomly assigned to a specialized tinnitus care group or a usual care group. Adult tinnitus sufferers referred to the audiological centre are eligible. Included patients will be followed for 12 months.

Primary outcome measure is generic quality of life (measured with the Health Utilities Index Mark III). Secondary outcomes are severity of tinnitus, general distress, tinnitus cognitions, tinnitus specific fear, and costs. Based on health state utility outcome data the number of patients to include is 198. Economic evaluation will be performed from a societal perspective.

Discussion/ Conclusion: This is, to our knowledge, the first randomized controlled trial that evaluates a comprehensive treatment of tinnitus and includes a full economic evaluation from a societal perspective. If this intervention proves to be effective and cost-effective, implementation of this intervention is considered and anticipated.

Background

Problem definition

THE CONDITION

Subjective tinnitus is the involuntary perception of the concept of a sound without the presence of an external source. It is a chronic condition that is highly prevalent, especially among hearing impaired individuals. Studies show a prevalence of 10% to 20% in the general population (Andersson, 2002), (Davies & Rafie, 2000) and among hearing impaired individuals prevalence has been estimated at 75% to 80% (Adams, Hendershot, & Marano, 1999). Of the Dutch population at least 2 million individuals suffer from some form of tinnitus, 340.000 individuals indicate to hear the tinnitus continuously and 60.000 individuals claim to be severely impaired in their daily activities (NIPO, 2002). Among severe sufferers it causes disability associated with severe affective problems, major declines in concentration, sleeping difficulties, hypersensitivity to sounds and problems in (re-)directing attention. The combination of these complaints makes them feel exhausted and frustrated resulting in diminished quality of life (El Refaie, et al., 2004; Erlandsson & Hallberg, 2000; Jastreboff, Gray, & Gold, 1996; Kroner-Herwig, Frenzel, Fritsche, Schilkowsky, & Esser, 2003; Scott, Lindberg, Melin, & Lyttkens, 1990). Tinnitus is known to occur as a concomitant of almost all the dysfunctions that involve the human auditory system (Andersson, 2002) and it is postulated that the aetiology of tinnitus is diverse and that different activation circumstances can be present (Cacace, 2003). Little is known about the pathophysiology and there is no known drug or curative therapy at present (Ahmad & Seidman, 2004).

THE HEALTH CARE PROBLEM

In many cases tinnitus sufferers are referred to different caregivers in a non-standardized way, and often receive insufficient and sometimes inappropriate treatment. This may comprise prescribing a drug that is not proven to be effective, or informing the patients that not much can be done to improve the situation. Especially in those individuals suffering from a moderate to severe tinnitus, incorrect information and delay of appropriate treatment is expected to increase psychological strain, aggravation of tinnitus severity and prolongation of the referral trajectory (Ahmad & Seidman, 2004). Since tinnitus sufferers seek help in various areas of health care without receiving appropriate treatment, they are financially burdening the system superfluously. In absence of a proven cure or uniformly effective treatment, tinnitus care is often fragmentised and costly (Lockwood, Salvi, & Burkard, 2002).

USUAL CARE

As for most health problems in the Dutch population, the general practitioner (GP) is the initial professional to consult for patients with tinnitus. In most cases, within six months after onset of subjective tinnitus the individual consults his GP, but one quarter of the respondents waits several years until they look for help (NIPO, 2002). In the official Dutch GP patient information letter on tinnitus (URL: www.nhg.artsennet.nl), it is stated that there is not much that can be done to alleviate complaints. Another frequently consulted specialist is the ENT physician. Treatment possibilities include the removal of cerumen, medication, and audiological rehabilitation. Generally, the effects of these treatments are disappointing.

MOTIVATION AND RELEVANCE FOR THE CHOSEN INTERVENTION

A recent study by El Refaie et al (2004) shows that functional and social handicap in tinnitus sufferers is significantly reduced, and quality of life improves significantly, as a result of attendance at a specialised tinnitus clinic. Specialised clinics for chronic disorders such as tinnitus and chronic pain have been proven to be most effective in treatment (Morley, Eccleston, & Williams, 1999). Similarities between tinnitus and chronic pain in terms of cognitive and behavioural mechanisms (Folmer, Griest, & Martin, 2001) have been suggested recently and a similar treatment could be effective for the tinnitus population. As in chronic pain, multidisciplinary specialised treatment is more effective in ameliorating severe tinnitus complaints than monodisciplinary treatments. A retrospective pilot study, by the applicants of this proposal, in the Tinnitus Centre Limburg (SC) shows significant improvements in 71% of the patients (N=41). Intrusiveness of the tinnitus ameliorates in 85% of the subjects and 78% experiences improvement in emotional distress caused by the tinnitus.

OBJECTIVE

The objective of this study is to examine the effectiveness, costs and cost-effectiveness of a comprehensive multidisciplinary treatment provided by a specialised tinnitus centre. Treatment is based on a stepped care approach, tailored to individual needs, with key elements from cognitive behavioural therapy, education, relaxation techniques, attention diversion, exposure in daily life situations, and tinnitus retraining therapy.

THE FOLLOWING RESEARCH QUESTIONS WERE FORMULATED:

1. What are the effects on generic quality of life of comprehensive specialized tinnitus care as provided by a specialised tinnitus centre, as compared to usual care?
2. What are the effects on health, in terms of negative affect, tinnitus beliefs, fear of the tinnitus, and tinnitus annoyance, of comprehensive specialized tinnitus care as provided by a specialised tinnitus centre, as compared to usual care?
3. What are the costs to health care and to society of treatment provided by a specialised tinnitus centre in the Dutch health care system as compared to usual care?
4. What is the cost-effectiveness of treatment provided by a specialised tinnitus centre in the Dutch health care system as compared to usual care?

Methods/design

Design

A randomised controlled clinical trial will be performed, with 2 conditions (see Figure 1). Patients will be assigned to a Usual Care (UC) Control condition or a Specialized Care (SC) condition. Both treatment conditions (UC and SC) will be provided by the Audiological Centre Hoensbroeck. Measures will be taken for blinding patients to treatment assignment. For assessing the cost-effectiveness, the SC care group will be compared only to the UC group and not to other treatment programs. The analysis will be performed from a societal perspective.

Participants

The study population consists of tinnitus sufferers referred to SC, with subjective tinnitus complaints, aged 18 years and older. Exclusion criterion is not being able to write and read in Dutch. Inclusion of patients started on September 1st 2007 and will proceed until the targeted number of patients is reached, for a maximum of 18 months. It is expected that enough patients will be referred to SC during this period to reach the necessary number as was calculated by power-analysis.

Sample size calculation and feasibility of recruitment

After attending a specialised tinnitus clinic a change of 0.065 in health state utility as measured with the SF-6D has been observed (El Refaie, et al., 2004). To detect this difference (assuming a two-sided significance level = 0.05, power= 80%, standard deviation of the difference = 0.15), 86 persons per group are needed. Taking into account 15% loss to follow up, the required sample size is 99 persons per group (198 persons in total). Approximately 400 individuals suffering from tinnitus apply to SC yearly. We expect this number to stay stable or even increase in the coming years. Therefore it is expected that it will not be necessary to actively recruit patients for this trial.

Patient allocation and randomization

Research information in written format and a declaration of willingness to participate in the trial will be sent to all new patients of the Tinnitus Centre Limburg that are registered with subjective tinnitus complaints. If a patient declares that he or she is willing to participate in the study they will be invited for the baseline measurement. This face-to-face contact will be used to determine whether the patients understood the information correctly and they a written informed consent will be obtained. If they agree, a hearing test will be performed to determine the amount of hearing loss and the patients are asked to fill in the tinnitus questionnaire (TQ) (McCombe, et al., 2001) to determine the severity of the tinnitus. Based on the Fletcher Index and the scores on the TQ the patient will be randomly assigned to one of the treatment groups. Since treatment depends on tinnitus severity and the severity of hearing loss it will be important that these two prognostic factors are equally presented in the UC group and the SC group.

Treatment allocation will be achieved by block randomisation (four blocks; A, B, C & D) to ensure equal and balanced groups. A randomization list was generated using randomization software. An equal number of patients will be allocated to the SC group and the UC group. Patients with a score equal to or less than 46 on the TQ and a Fletcher Index below 60 dB will be allocated to block A. Patients with a score equal to or less than 46 on the TQ and a Fletcher Index equal to or above 60 dB will be allocated to block B. Patients with a score above 46 on the TQ and a Fletcher Index below 60 dB will be allocated to block C. Finally, patients with a score equal to or below 46 on the TQ and a Fletcher Index above or equal to 60 dB will be allocated to block D. The randomization procedure will be performed by an independent person at a location outside SC.

Intervention

The intervention consists of comprehensive tinnitus management provided by a specialized tinnitus centre in the health care system. The tinnitus centre offers care following a stepped-care approach with two levels (see Figure 1). Stepped care is a framework for organizing health services based on patients' needs, with a gradual increase in the intensity of the care at each level (Von Korff, 1999).

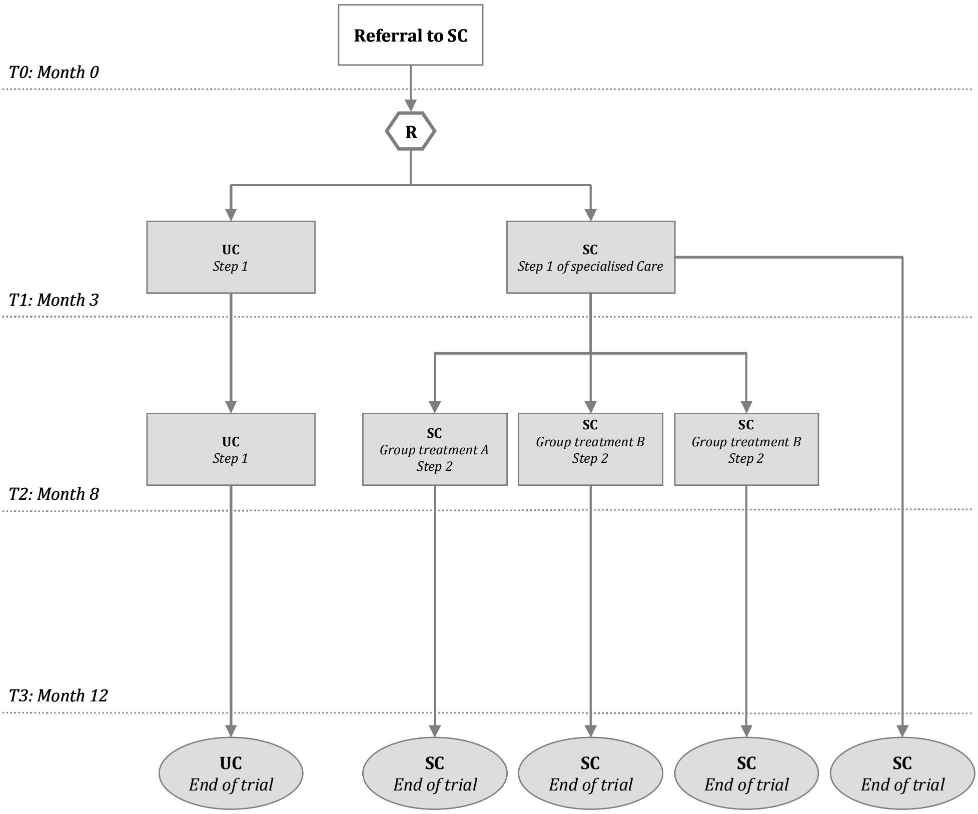
The first step of intervention consists of a basic multidisciplinary intervention for all patients allocated to SC. This multidisciplinary intervention consists of audiological diagnostics and intervention (see table 1 for specifics), a tinnitus educational group session and an individual consult with a clinical psychologist. For patients with mild complaints this basic intervention is expected to suffice.

For patients with moderate to severe complaints a second step of intervention exists. This second step consists of combinations of the following therapies: Cognitive Behavioural Therapy (CBT), Attentional training (AT) by means of movement therapy to build up a more positive mind-body relationship, exposure techniques, and Relaxation Therapy (RT). The programs are preferably offered in group format. The group treatments are based on the theoretical framework of the fear-avoidance model proposed by Lethem and colleagues (Lethem, Slade, Troup, & Bentley, 1983), refined by Vlaeyen and

Linton (Vlaeyen & Linton, 2000), and a cognitive behavioural model by Kröner-Herwig (Kroner-Herwig, et al., 2003) explaining factors in the development and maintenance of chronic tinnitus. Based on existing knowledge in chronic pain management, Folmer et al (Folmer, et al., 2001) formulated treatment strategies possibly effective for patients suffering from chronic tinnitus, or as they put it, chronic phantom "pain". The authors conclude that severity of depression, anxiety and insomnia is highly correlated with the severity of the tinnitus, similar to chronic pain. They suggest that techniques and strategies effective in treating chronic pain disorder might be useful in treating tinnitus as well. These include: stress management techniques (including relaxation therapy) to reduce physiological reactivity, cognitive-behavioural techniques to reduce catastrophising cognitions and reduce avoidance behaviours and exposure to fear-eliciting stimuli to adjust for estimations of the tinnitus sound. The step 2 consists of three main treatment options namely; program A for patients suffering from tinnitus on a moderate to severe level, program B for severe tinnitus complaints, and program C for the severely hearing impaired suffering from tinnitus.

TABLE 1 . AUDIOLOGICAL DIAGNOSTICS AND INTERVENTION STEP 1 IN SPEICALISED CARE

Audiological diagnostics and intervention	
1	Pure tone and speech audiometry
2	Uncomfortable Loudness Level measurement
3	Tympanometry: including stapedial reflexes
4	Hearing aid check and optimisation (if present)
5	Tinnitus analyses: Pitch Mask Frequency and Masking level
6	Tinnitus anamnesis using structured questionnaire
7	Individual consult by clinical physicist in audiology (60 minutes)



UC = Usual Care as provided throughout the Netherlands; SC = Specialized Care, T0 = baseline; T1, 2, and 3: Follow up time points

FIGURE 1. THE TRIAL DESIGN; USUAL CARE (UC) COMPARED TO SPECIALIZED CARE (SC) A STEPPED CARE APPROACH

All programs are based on the principals stated above. Depending on severity of complaints and hearing loss, group treatment is more intense and tailored to individual needs. In a review by Andersson and Lyttkens (Andersson & Lyttkens, 1999) it was concluded that offering cognitive behavioural coping techniques in combination with relaxation exercises received the most empirical support.

Usual Care

Usual care consists of a standardized version of the treatment that is currently applied in peripheral audiological centres throughout the Netherlands for tinnitus patients. A telephone survey was conducted amongst all audiological centres (n=28) in the Netherlands. The results of this survey determined the content of the usual care treatment protocol in the current study. The treatment consists of audiological diagnostics and intervention and, if necessary, one or more consultations with a social worker with a maximum of ten one hour sessions.

Outcomes and instruments

PRIMARY OUTCOME MEASURE:

Generic quality of life, as measured with the Health Utilities Index Mark 3 (HUI3) (Horsman, Furlong, Feeny, & Torrance, 2003)

SECONDARY OUTCOME MEASURES:

Anxiety and depression as measured with the Hospital Anxiety and depression Scale (HADS) (Spinhoven, et al., 1997);

Tinnitus related disability and handicap, as measured with the Tinnitus Handicap Inventory (THI) (Newman, Jacobson, & Spitzer, 1996);

Tinnitus annoyance and severity, as measured with the Tinnitus Questionnaire (TQ) (McCombe, et al., 2001);

Tinnitus-related fear is assessed by the Fear of Tinnitus Questionnaire (FTQ). This novel 17-item questionnaire is based on the Tampa scale for Kinesiophobia (Roelofs, et al., 2007), and the Pain Anxiety Symptoms Scale (McCracken, Zayfert, & Gross, 1992);

Dysfunctional beliefs and/or cognitions regarding the tinnitus, as measured with the Tinnitus Coping and Cognition list (TCCL). The TCCL is a recent adaptation of the Pain Coping and Cognition Questionnaire (Stomp - van den Berg, et al., 2001);

Catastrophic (mis)interpretations of tinnitus are measured with the Tinnitus Catastrophising Scale (TCS). The TCS is a recent adaptation of the Pain Catastrophising Questionnaire (Sullivan, Bishop, & Pivik, 1995);

Costs are measured with a retrospective cost questionnaire.

Data collection

Measurement of the HUI3, TQ, THI, HADS, FTQ, TCCL, TCS and a cost questionnaire will take place at four moments during a 12 month period. At baseline (T0) the questionnaires will be completed at the audiological centre in the presence of research assistance. Three (T1), eight (T2) and twelve (T3) months after baseline the patient will be able to complete the questionnaires at home through the internet. Login codes will be sent to their home address two weeks in advance. If patients are incapable of completing the questionnaire through the internet, a paper version will be provided. Non-responders will receive a telephone call as a reminder to complete the questionnaires. If they do not wish to further participate in the study, the reasons for their withdrawal will be recorded.

Data-analysis

Intention-to-treat analysis will be performed, including all patients that were originally enrolled in the study, irrespective of whether they completed the therapy. To test the differences between the conditions, mixed multilevel regression analyses will be used with a hierarchical backward elimination method. The analysis will be carried out for the post-treatment assessments (after level 1 and level 2 respectively) and follow-up data of the outcome variables. The independent variables are: pre- measurements of the dependent variable, treatment condition, treatment centre, socio-demographics, tinnitus-related variables, and the interaction variable pre-measurement*treatment. The treatment condition always remains in the regression model, but the other independent variables will be added to increase the power of the analysis and are subsequently eliminated to keep only the significant ones. At each step of the analysis, tests will be done to check for high co-linearity (VIF>10) and/or outliers (Cook's Distance (Cook D) and Studentised Residual (Sresid)). If Cook’s D is smaller than 1, the case will be removed from the analysis. If Sresid < -3 or > 3, the case will be removed providing that Cook D of this case is considerably higher than from the other cases. By looking at plots of the relationship between each independent variable and the dependent variable, a possible curvilinear relationship is excluded. The prediction errors will be also checked for normality (zresid). For each dependent variable, the initial regression model includes all independent variables and interaction mentioned above. Non-significant interactions (p>.05) will be deleted from the model. Next, non-significant (p>.10, two-tailed) predictors will be deleted one by one, except the treatment factor that always remains in the model. If a significant interaction is found, the treatment effect will be evaluated within strata defined by the covariate interacting with the treatment.

Based on the results of the intention-to-treat analysis, additional per protocol analysis will be performed, incorporating only those patients that completed the therapy. The same analyses as according to the intention-to-treat principle will be performed with respect to the primary outcomes.

Economic Evaluation

A cost-effectiveness analysis will be performed from a societal perspective. Since both effects on costs and generic health-related quality of life are to be expected, the method of economic evaluation is a cost-utility analysis. The primary effect parameter is generic health-related quality of life, measured in quality adjusted life years (QALYs). The time horizon of the study is one year, identical to the duration of the follow up in the clinical study. The immediate treatment effects (measurements at 3 and 6 months) and short-term treatment effects (measurement at 12 months) are observed in this study. It is not possible to observe long-term treatment effects (longer than12 months), since the duration of the study is limited to three years. Discounting is not relevant given the one-year time horizon. Sampling uncertainty surrounding the incremental cost-utility ratio will be estimated by non-parametric bootstrapping. Confidence intervals for the incremental cost-utility ratio will be calculated from the bootstrap results. The implications of sampling uncertainty on decision uncertainty (the probability specialised tinnitus care provided in a specialised tinnitus centre is more cost-effective than usual care) will be quantified using the cost-effectiveness acceptability curve. Sensitivity analyses will be used to show the impact of variation in non-stochastic input parameters on the incremental cost-utility ratio, such as discount rate, unit prices, and design issues. The impact of variability on the incremental cost-utility ratio arising from diversity and heterogeneity in the patient population will be examined in subgroup analyses. Costs in the analysis include direct health care costs (medical costs for prevention, diagnostics, therapy, rehabilitation and care), direct non-health care costs (travel costs) and indirect costs (productivity loss). Resource use will be measured using the case-record forms and 3 monthly retrospective cost-questionnaires. In the cost questionnaires the PRODISQ modules will be used to estimate productivity loss (Koopmanschap, 2005). When available, the standard unit costs from the Dutch Manual for Cost Analysis (Oostenbrink, Bouwmans, Koopmanschap, & Rutten, 2004) will be used. Resource use for which no standard unit costs are available will be valued using integral cost calculations. Costs from productivity loss will be quantified using the friction cost method, as recommended in the Netherlands (Oostenbrink, et al., 2004).

Ethical considerations

Patients will be informed verbally and in written format about the research project before they sign the informed consent form. Participants can retreat from the study at any moment. This will have no influence on their further treatment. The study protocol has been reviewed and approved by the Medical Ethical Board of the Rehabilitation Foundation Limburg. The scientific merits of the study protocol have been reviewed in the consecutive phases of research funding process by the independent reviewers of the funding organization ZonMw, the Netherlands Organization for Health Research and Development.

Funding

A grant was obtained in a competitive application process of the efficacy research program, round 2006, of the Netherlands Organization for Health and Development ZonMw.

Discussion

Potential strengths of the study protocol

DESIGN

To our knowledge this is the first randomized controlled clinical trial that evaluates a comprehensive multidisciplinary treatment of tinnitus versus care as usual. A particular strength is the randomization procedure, in which allocation is concealed. Randomization is done at the patient level and stratified on degree of hearing impairment and tinnitus severity. This procedure is performed by an external independent person.

SAMPLE SIZE

To our knowledge this is the first study evaluating a comprehensive multidisciplinary treatment of tinnitus that includes a large sample size. At least 198 patients with tinnitus will be included in the study. As a result most statistical procedures will be robust against violations of assumptions that have to do with normality.

RECRUITMENT STRATEGY

In this randomized controlled trial every recruited patient experiences tinnitus to be one in three of their major complaints. Since tinnitus does not have to be the primary problem it is ascertained that different severity levels of tinnitus will be evaluated in this study.

COMPETENCE OF HEALTH CARE PROFESSIONALS

Every discipline is trained to perform the intervention in a uniform way. To get insight into their actual performance, every professional is required to register all activities during all treatment-related activities during patient visits. This registration will be used to search for factors related to the intervention that might influence effectiveness.

Potential limitations of the study protocol

INTERVENTION

There is no uniform way of treating tinnitus in the audiological centres in the Netherlands. In order to model usual care treatment, a telephone survey was conducted amongst all audiological centres. This implicates that the currently implemented form of usual care is standardized, whereas in real practice clinical variation in treatment is expected.

RANDOMIZATION APPROACH

Randomization on patient level could lead to contamination, and bias the results of this study. However, the influence of contamination is minimised since patients in the usual care group have no access to the intervention offered by SC-specialist and vice versa. Nevertheless it is possible that specialists that provide the usual care treatment are more attentive to the usual care group than would be expected if treatment was provided in an independent centre. As a result our findings may be conservative.

Conclusion

This study will provide information on whether a comprehensive, multidisciplinary treatment is more effective and efficient care for tinnitus patients. The results will also show whether the specialised treatment improves quality of life and patient satisfaction. If the intervention is proven to be effective, implementation of the intervention is considered and anticipated. First results are not expected before the beginning of 2010.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors have read and approved the final manuscript. RC, the researcher and first author of this manuscript, is involved in the development of the experimental intervention, the design of the study, data collection, and statistical analyses and performed the power calculation. MJ is involved in the design of the study, wrote the economic evaluation part of the study protocol, supervises the economic evaluation, the planning and the project and is involved in revising the article for important intellectual content. IM was helpful in writing this manuscript and is involved in the design of the study, the data collection and the statistical analysis for the economic evaluation part of the study. DS is involved in the development of the experimental intervention, the design of the study and the instruction of the health care professionals regarding this intervention. AER and DB gave advice regarding the study protocol and are involved in revising the study protocol for important intellectual content. JV and LA supervise the project and are involved in the development of the experimental intervention, the design of the study and revising the study protocol for important intellectual content.

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CHAPTER VI

EFFECTIVENESS OF STEPPED TINNITUS CARE; CBT-BASED TREATMENT VERSUS CARE AS USUAL

Based on

Cima, R.F.F., Maes, I.H., Joore, M.A., Scheyen, D.J.W.M., El Refaie, A., Baguley, D.M., Anteunis, L.J.C., van Breukelen, G.J.P., Vlaeyen, J.W.S. (2012). Specialised treatment based on cognitive behaviour therapy versus usual care for tinnitus: a randomised controlled trial. *The Lancet, 379* (9830), 1951-1959.

Abstract

Background Up to 21 percent of the adult population has at least once in their lifetime been bothered by tinnitus, which is one of the most distressing and debilitating audiological problems. The lack of medical cures and standardized practice often result in costly and prolonged referral trajectories, and unnecessary suffering. A stepped-care approach, with a basic cognitive behavioural therapy program for all patients, and a follow-up approach for patients with more severe tinnitus complaints, is presently investigated.

Methods 741 adults (> 18 years) with a primary complaint of tinnitus were assessed for eligibility to enter a randomized controlled trial, comparing Specialist Care (SC) consisting of cognitive behavioral therapy (CBT) with elements of sound-focused tinnitus retraining therapy (TRT) with Usual Care (UC). Primary outcomes were Health related Quality of life (HUI), Tinnitus Severity (TQ), and Tinnitus impairment (THI), which were assessed pre-treatment, and at 3, 8 and 12 months after randomization. Multilevel Mixed regression was used for intention to treat analyses; final analysis included all participants for whom we had baseline data on primary and secondary outcomes. This study is registered; number NCT00733044.

Findings 492 patients, blinded for treatment allocation, were randomly assigned to either UC (n=247) or SC (n=245), pre-stratified on tinnitus-severity and hearing impairment, completed baseline measurements, and were included in final analyses. Overall, adjusted mean changes were higher in the SC group than in the UC group at 12 months for HUI (between-group difference=0·059 [95% CI 0·025 -0·094]), TQ (between-group difference=-8·062 [95% CI -10·829 -5·295]) and THI (between-group difference=-7·506 [95% CI -10·661 -4·352]), with effect sizes of 0·24, 0·43 and 0·45 (Cohen's d) respectively. Moreover, SC generates greater improvements in general negative emotional states, level of tinnitus-related catastrophic thinking, and tinnitus-related fear than UC. Additionally, the treatment was effective irrespective of initial tinnitus severity levels. No adverse events or harmful side-effects were reported throughout the trial.

Interpretation A specialized CBT-based treatment might be the treatment of choice for milder forms of tinnitus suffering as well as for more severe tinnitus incapacitation, and hence may be considered for widespread implementation.

Introduction

Sixteen to 21 percent of the adult population is at one point in life bothered by tinnitus, (Krog, Engdahl, & Tambs, 2010) the perception of a noxious disabling internal sound without an external source. Although often not recognized by the general public, tinnitus is one of the most distressing and debilitating audiological problems, affecting almost all aspects of daily life (Cima, Vlaeyen, Maes, Joore, & Anteunis, 2011; Javaheri, Cohen, Libman, & Sandor, 2000). Cognitive impairments and negative emotions associated with tinnitus are shown to be most troubling for patients and their families (El Refaie, et al., 2004; Hallam, McKenna, & Shurlock, 2004).

Since tinnitus is not easily objectified, and medical curative efforts have been unsuccessful, the effective management of tinnitus complaints has been a challenge, requiring a multitude of disciplines and usually prolonged trajectories (Cima, et al., 2009). Evidence for a uniformly successful treatment of tinnitus is lacking, and current usual care practices for tinnitus primarily consist of fragmentized interventions; often resulting in communicating to patients that nothing can be done about the tinnitus, but learn to live with it (Cima, et al., 2009). The lack of standardized practice presents difficulties in unifying assessment, treatment, identifying subsets of patients with differential clinical demands, and in comparing clinical and research outcomes (Hoare, Gander, Collins, Smith, & Hall, 2012).

Two main tinnitus-treatment approaches can be distinguished. First, sound-based therapies, such as tinnitus retraining therapy (TRT), involve tinnitus-masking methods on the sound-perception-level in combination with structured counselling sessions (Phillips & McFerran, 2010); (Jastreboff & Hazell, 2004)). This approach, commonly based on Jastreboff's neuro-physiological model (Jastreboff & Hazell, 1993), is aimed at ameliorating tinnitus distress, through education and exposure to a neutral external sound. By habituating tinnitus-patients to this neutral sound, which is hypothesized to generalize to the threatening tinnitus-sound, tinnitus annoyance is expected to diminish. Supporting evidence for the TRT approach is scarce, and most of the published reports derive from retrospective and uncontrolled trials (Hiller & Haerkötter, 2005; Hoare, Kowalkowski, Kang, & Hall, 2011; Hoare, Stacey, & Hall, 2010; Phillips & McFerran, 2010). A second main approach is cognitive behavioural therapy (CBT) for tinnitus (Kroner-Herwig, Frenzel, Fritsche, Schilkowsky, & Esser, 2003; Martinez Devesa, Waddell, Perera, & Theodoulou, 2007; Zachriat

& Kroner-Herwig, 2004). CBT is a more comprehensive form of psychotherapy aimed at modifying dysfunctional beliefs and behaviours. Typically, CBT for tinnitus includes psycho-education, relaxation, exposure-techniques, and behavioural reactivation, often in combination with mindfulness-based training. Although, CBT-based tinnitus-treatment approaches have shown to reduce suffering and improve quality of life, large scale and well-controlled trials are still needed (El Refaie, et al., 2004; Hesser, Weise, Westin, & Andersson, 2011; Kroner-Herwig, et al., 2003; Martinez Devesa, et al., 2007). The premise that the intensity of CBT-treatment can vary depending on severity of tinnitus-complaints, has never been tested.

We developed a novel multidisciplinary tinnitus-treatment protocol; a stepped-care CBT based approach with elements from TRT. A stepped-care approach is a framework for organizing health- services based on individual patients' needs, with a gradual increase in the intensity of the care at each level (Von Korff & Moore, 2001). The main aim of the current study was to investigate the effectiveness of this new specialised tinnitus-treatment protocol versus care as usual, using a randomized controlled design (Cima, et al., 2009).

Methods

Aims and hypotheses

We hypothesized that [a] Specialised care (SC) would be more effective than Usual Care (UC) in increasing generic health-related quality of life, reducing distress caused by the tinnitus, and reducing tinnitus-related impairment, and [b] SC would be more effective than UC in reducing general negative affect, the level of catastrophic mis-interpretations of tinnitus, and tinnitus-related fear.

Study design

A two group, 2- stepped care, single-centre randomized controlled trial was carried out with adult tinnitus patients, with 3 follow-up assessments at 3, 8 and 12 months after randomization (see web-appendix B for specifics on data collection). Tinnitus patients referred to our centre were invited for a first off-centre baseline assessment contact, after which they were randomly allocated to either Usual Care (UC) or Specialized Care (SC). The Medical Ethical Board of the Rehabilitation Foundation Limburg reviewed and approved of the study protocol (METC-SRL: 11/09/2006) and trial funding was supported by Netherlands Organization for Health Research and Development (ZonMw, Reg. number: 945-07-715). The trial has been registered at ClinicalTrial.gov (Reg. number: NCT00733044).

Participants

Adult patients referred to our centre with a primary complaint of subjective tinnitus were eligible for inclusion. Patients were excluded when unable to read and write in Dutch, when health problems, such as terminal illness or physical problems impairing travelling to our centre, prevented participation, and when they had undergone treatment at our centre within 5 years prior to trial enrolment. Patients were assessed by an ENT-physician to rule out otological pathology requiring immediate medical care. Informed consent was obtained before assessment and trial-entry; both patients and assessors were blinded for treatment allocation.

Randomization and blinding

Treatment allocation was by randomization, pre-stratified on both tinnitus-severity (stratification cut-off point at 47 points on the tinnitus questionnaire) and hearing impairment (stratification cut-off point at the pure-tone average (PTA) of 60 dB hearing level in worst ear), giving four strata. Within each stratum, patients were randomized to one of both treatment arms in blocks of 4 patients. The randomization procedure was performed by one of the independent research assistants at an off-centre location, after receiving informed consent and baseline assessment.

Patients were blinded for treatment allocation. Prior to trial enrolment patients were informed they would be allocated to one of two different treatments, aimed at tinnitus management, using a client-centred, stepped-care approach. They were also aware that by giving their consent they would not be informed as to which treatment they were allocated to. Early in the intervention-procedure detailed information about the treatment received was unveiled, while the participants remained blind to the content of the alternative treatment.

Intervention-procedures

SYSTEMATIC REVIEW

Panel 1 provides a systematic review on current treatment approaches in tinnitus management. The combination of two main theoretical models and treatment approaches was found to be novel, and not studied before (Cima, et al., 2009).

OVERVIEW

Both UC and SC were setup in a stepped-care manner (see figure 1). Both step-1 and step-2 in UC and SC were finalized after 8 months followed by a no-contact period of 4 months up until the last follow-up assessment. Step-2 treatment had a duration of 12 weeks maximally in both UC and SC. Case Report Forms (CRF) were used for each patient to standardize treatments and for trial purposes, replacing the medical charts. Each CRF included extensive protocols for each separate professional, including supporting staff, and for multidisciplinary patient-related activities.

CARE AS USUAL (UC)

The UC procedure entailed a standardized protocol modelled after the average care as is usually provided by secondary-care audiological centres across the Netherlands. A qualitative study was carried out by means of a telephone survey, including all audiological centres (n=26) currently operative in the Netherlands. The number of professionals involved and counselling hours were averaged and discipline-type and health-care activities were categorized by two independent raters, resulting in the UC treatment protocol (see PANEL 2).

Step-1 of UC treatment consisted of a standard audiological intervention. For patients with mild complaints, treatment ended after the first step, while they remained in the trial for follow-ups. When tinnitus suffering was more severe (as measured at baseline and after audiological counselling), patients entered step-2 treatment.

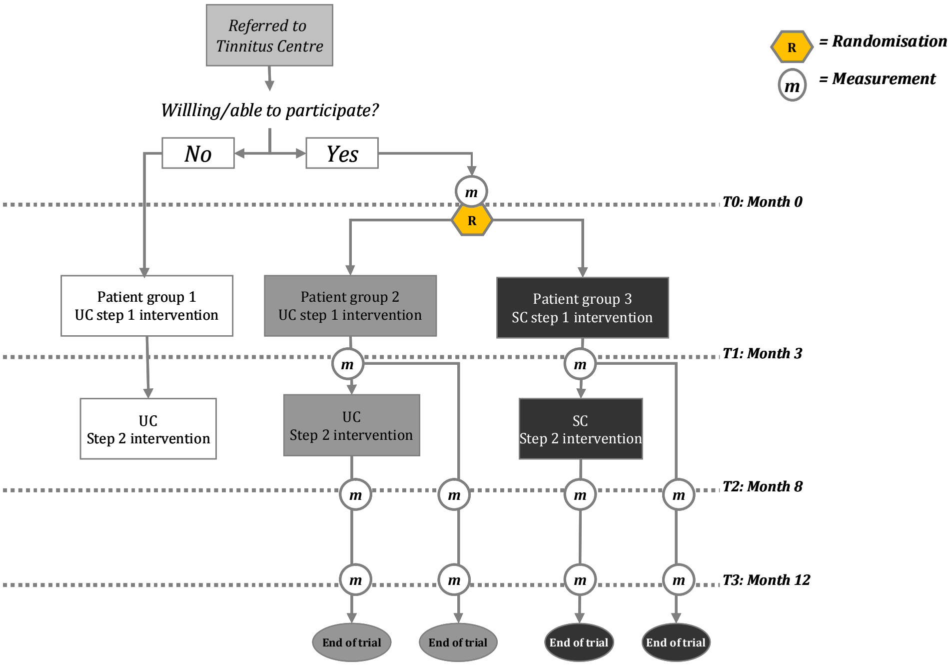
PANEL 1: Research in Context; a Systematic Review

A rather broad range of search terms to include all relevant studies performed on tinnitus and group treatment. All Systematic reviews, reviews, and meta analyses were included as well. Search terms: Tinnitus AND Trial AND review (OR management OR care, OR specialised clinic,, OR multidisciplinary, OR therapy, OR treatment, OR systematic, OR meta analysis, OR cognitive behavioural, OR psychological, OR relaxation OR education OR quality of life, OR stress, OR distress, OR coping, OR anxiety, OR depression, OR chronic, OR pain, OR costs, OR cost analysis, OR effects, OR outcome assessment OR sound therapy OR TRT) NOT (Complementary Therapies, OR Acupuncture, OR Ginko biloba, OR surgery, OR pharmacology). It is important to note that he second search term 'Trial' includes studies using other methodological designs than RCT only, this according to the MeSH thesaurus. Population: Adult tinnitus population. Intervention: Multidisciplinary care, specialised clinic, cognitive behavioural therapy, psychological treatment, relaxation, education, tinnitus retraining, TRT (sound therapy). Outcome Measures: Quality of life, stress/distress, depression, anxiety, coping. Tinnitus distress/handicap/impairment. Methodological filters: Systematic review, RCT, follow-up of cohort design, case control study. Databases: Medline (1980 – present), Psychinfo (1972-present), Psyarticles, Cinahl (1982 – 2005), ERIC database (1966 – 2005/09), Econlit, DARE database, Education Resources Information Centre, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Controlled Trials Register, Cochrane Methodology Register, NHS Economic Evaluation Database, Health Technology Assessment Database, Cochrane Database of Methodology Reviews (CDMR). Number of manuscripts retrieved: After performing the first search strategy described above a total number of 216 manuscripts were retrieved (Medline: 125; Psychinfo: 20; Psyarticles: 3; Cinahl: 14; ERIC: 11; Econlit: 2; DARE: 36; Cochrane: 5). Validity assessment: Two independent reviewers assessed all studies for inclusion quality. Included were: systematic reviews, meta analyses, reviews, RCT's and other trials comparing different treatment combinations based on group treatments, including behavioural modification, relaxation, attention diversion and exposure, biofeedback, coping strategies, specific tinnitus management programmes, and multidisciplinary approaches. Not included were studies on pharmacological treatment, complementary or alternative treatments, and studies based on animal-models and neuro-magnetic stimulation. Results: The total amount of selected manuscripts was 22, of which 8 systematic reviews, 9 RCT studies, 3 follow-up or case control studies, and 1 controlled but not randomized and 1 evaluation of current practice.

INTERPRETATION

The combination of 2 main theoretical models, and treatment approaches, Cognitive Behavioural Therapy (CBT) and Tinnitus Retraining therapy (TRT) was found to be novel. CBT for tinnitus seems the most promising approach in diminishing tinnitus related distress and decrease main complaints of patients. The use of sound generating devices, whether masking devices, wearable players or hearing aids, even when combined with directive counselling sessions, have of yet not been proven to be effective as a single treatment approach (as is the case in TRT based approaches); effects seem modest at best. Treatment strategy might be best organized integrally, using a standardized approach in diagnostics, treatment and assessments because of the fact that using the approaches serially and at random might lead to unwanted increase of health utilization and costs. Moreover, a CBT based framework in tinnitus management is advisable.

[FIGURE 1.. FLOWCHART



Patient group 1: Patients not able or willing to participate, Patient group 2: Patients who were allocated to UC, Patient group 3: Patients who were allocated to SC, UC: Usual Care, SC: Specialised Care

PANEL 2. Usual Care Treatment protocol

	Contact (min)	Professional	Activities
Step 1 (T0 – T1)	Audiological diagnostics (105)	Audiological assistant	Pure tone and speech audiometry, Tympanometry (stapedial reflexes) Tinnitus analyses: Pitch Mask Frequency and Minimum Masking Level Uncomfortable Loudness Level measurement Hearing aid check and optimisation (if present) Questions about duration and location of the tinnitus
		Clinical physicist in audiology (CPA)	Individual consult by clinical physicist in audiology Audiological anamnesis Assessment of audiometry and explanation Information about tinnitus and hearing loss Assessment severity of complaints *When indicated by hearing loss:* Prescription hearing aid, *When indicated by patient:* Prescription tinnitus masker*
	Audiological rehabilitation (30)	Audiology assistant	Check up after 8 weeks of hearing aid-usage Hearing aid check and optimisation
	Audiological follow-up (40)	Audiology assistant	Pure tone and speech audiometry, Tympanometry (stapedial reflexes) Uncomfortable Loudness Level measurement Hearing aid check and optimisation (if present) Tinnitus analyses: Pitch Mask Frequency and Minimum Masking Level
		CPA	Individual consult by clinical physicist in audiology When indicated: Referral to social work
Step 2 (T1 – T2)	Intake Social work (60)	Social worker	General inventory of complaints and use of hearing aids/maskers When indicated: Social work trajectory of maximum 9 follow-up contacts
	Follow-up Social work (60)	Social worker	Maximum 9 contacts including Counselling sessions Telephone contacts Extraneous appointments with third parties House calls

* Sound-generators were prescribed when specifically asked for by the patient, and were fitted by using a small band noise around the Pitch Match Frequency presented slightly below the tinnitus masking level.

SPECIALISED CARE (SC)

The first step of SC-treatment consisted of multidisciplinary diagnostics and specific TRT-based counselling elements, carried out in a cognitive behavioural framework (including audiological rehabilitation when necessary). For patients with mild complaints this basic intervention was expected to suffice, and they were measured for follow-ups only. When tinnitus suffering was more severe (as measured at baseline and after psychological screening), patients entered step-2 treatment, which consisted of three 12-week group-treatment options; Program A for patients suffering from tinnitus on a moderate to severe level, Program B for severe tinnitus complaints, and program C for severely hearing impaired tinnitus patients (see PANEL 3).

Treatment fidelity

Treatment fidelity was assessed by a post-hoc investigation of CRF's, patient-attendance lists, and electronic databases, on a random sample of 40 cases per condition, in order to verify whether both UC and SC were performed according to treatment-protocols (adherence), and not overly influenced (contamination) by contrasting elements from the other treatment (Leeuw, Goossens, de Vet, & Vlaeyen, 2009). See appendix B for specifics on data collection.

PANEL 3. Specialized Care Treatment protocol

	Contact (min)	Professional	Activities
Step 1 (T0 – T1)	Audiological diagnostics (105)	Audiology assistant	Pure tone and speech audiometry, Tympanometry (stapedial reflexes) Tinnitus analyses: Pitch Mask Frequency and Minimum Masking Level Uncomfortable Loudness Level measurement Hearing aid check and optimisation (if present) Tinnitus anamnesis using structured interview
		Clinical physicist in audiology (CPA) (trained in TRT counselling)	Individual consult by clinical physicist in audiology ** Audiological anamnesis, Assessment of audiometry and explanation Information about tinnitus and hearing loss Introduction to the neurophysiological model (Jastreboff, 1990) Reading materials and treatment rationale are provided Explanation of treatment protocol in the first step and explanation of stepped-care approach When indicated by hearing loss: Prescription hearing aid, When indicated by patient: Prescription sound generator*
	Audiological rehabilitation (30)	Audiology assistant	Check up after 8 weeks of hearing aid/masking device -usage Hearing aid check /masking device and optimisation
	Tinnitus educational session (120) Max. 10 patients with partner	Psychology Assistant	The basics of the TRT are explained The NF model is explained extensively Fear-avoidance is discussed General information about second step care is provided Patients are enabled to have a group discussion and ask remaining questions
	Intake Psychology: Extensive tinnitus specific and general psychological diagnostic anamnesis (60).	Clinical psychologist	When indicated by scores on TQ, THI and anamnesis; Treatment goals for step 2 are formulated in concordance with patient and the patient is planned in multidisciplinary team meeting
	Audiological follow-up (40)	Audiology assistant	Pure tone and speech audiometry, Tympanometry (stapedial reflexes) Tinnitus analyses: Pitch Mask Frequency and Minimum Masking Level Uncomfortable Loudness Level measurement Hearing aid check and optimisation (if present)
		CPA (TRT)	Individual consult by clinical physicist in audiology **
	Multidisciplinary team meeting (10/patient)	All professionals involved in SC	All tinnitus patients are discussed and, when indicated by scores on TQ/THI and clinical view of psychologist, multidisciplinary treatment goals for step 2 are integrated in a plan of treatment
Step 2 (T1 – T2)	Group treatments A, B, or C (120/session) Duration of 12 weeks	Clinical psychologist Movement therapist Physical therapist CPA Social worker Speech-	1. Group sessions: (intensity varies across group-treatments A, B, and C)) CBT; Psycho education, cognitive restructuring, exposure techniques, mindfulness-based elements, stress relieve & attention redirecting techniques by means of movement therapy, and applied relaxation 2. Themed group counselling sessions (including partners)

	therapist	
Individual Trajectory in case of contra indication for group treatment (60/per discipline)	Clinical psychologist Movement therapist	Combination of the above mentioned group treatment principles applied on individual basis (With optional addition of a combination of professionals involved in group treatments)

* Sound-generators were prescribed when specifically asked for by the patient and were fitted by using a small band noise around the Pitch Match Frequency, presented slightly above hearing threshold, as measured with the small band noise of the sound generator.

** Specifically the counselling elements of TRT were part of intervention; educating patients about tinnitus and the neuro-physiological model

Outcomes

STRATIFICATION ASSESSMENT

To assess *hearing impairment,* pure tone audiometry was performed bilaterally on 1, 2, and 4 kHz, using a mobile audiometer (Interacoustics AS208) with audiometry headphones (Telephonics TDH-39, Peltorcapped) and the PTA for 1, 2 and 4 kHz (stratification cut-off point at 60 dB hearing level in worst ear) was calculated. The Tinnitus Questionnaire was used to assess Tinnitus-severity at baseline (stratification cut-off point at a score of 47) (Rief, Weise, Kley, & Martin, 2005).

PRIMARY OUTCOME MEASURES

The HUI mark III is a 17-item questionnaire to assess Health-related quality of life or Generic Health on eight dimensions: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain/complaints. Each question has five or six levels, and 972.000 possible health states can be computed. Possible utility scores range from -0·36 to 1·00 for the HUI mark III (Feeny, et al., 2002). The HUI has shown adequate responsiveness in the tinnitus population (Maes, Joore, Cima, Vlaeyen, & Anteunis, 2011).

Tinnitus-severity was assessed by the Tinnitus Questionnaire (TQ) (Hallam, Jakes, & Hinchcliffe, 1988). The TQ consists of 52 items rated on a 3-point scale and assesses psychological distress associated with tinnitus. Psychometric properties of the TQ have proven excellent in different languages (Meeus, Blaivie, & Van de Heyning, 2007).

The tinnitus Handicap Inventory (THI) is a 25 item instrument scored on a 3-label category scale. The THI assesses *Tinnitus-related impairment* on 3 domains; functional, emotional and catastrophic (Newman, Jacobson, &

Spitzer, 1996); (Newman, Sandridge, & Jacobson, 1998); (Bartels, Middel, van der Laan, Staal, & Albers, 2008). Both overall and subscale internal consistency were found to be satisfactory in the current sample.

SECONDARY OUTCOME MEASURES

Negative Affect was measured with the Hospital Anxiety and Depression Scale (HADS), which contains 14 items and has good reliability and validity (Spinhoven, et al., 1997). The Tinnitus Catastrophizing Scale (TCS) is an adapted version of the Pain Catastrophizing Scale (Van Damme, Crombez, Bijttebier, Goubert, & Van Houdenhove, 2002).

The TCS assesses *catastrophic mis-interpretations of the tinnitus sound* and has 13 items to be rated on a 5-point scale (0 = not at all, 4 = always). The TCS has been tested with patients (Cima, Crombez, & Vlaeyen, 2011), and internal consistency of the total TCS score in the current sample was excellent (Cronbach's alpha = ·94).

The Fear of Tinnitus Questionnaire (FTQ) measures *Tinnitus-related fear*. Some of the FTQ items were derived from the Tampa Scale for Kinesiophobia and the Pain Anxiety Symptoms Scale (Roelofs, et al., 2007); (McCracken, Zayfert, & Gross, 1992) The FTQ was pre-tested with patients (Cima, Crombez, et al., 2011), and has 17 items to be rated on a true or false scale. Internal consistency of the total FTQ score in the current sample was excellent as well (Cronbach's alpha = ·82).

Demographic data were gathered by a 5-item questionnaire to establish gender, age, duration of complaints, educational level and adherence area.

Sample size

Only one study on quality of life of tinnitus patients receiving specialized tinnitus care was identified. The observed change of 0·065 in health state utility score in that study (El Refaie, et al., 2004), with a standard deviation of 0·15, as measured with the Short Form-36, (Hays, Sherbourne, & Mazel, 1993) was used to calculate our sample size. Given $\alpha = 0{\cdot}05$ (2-sided) and power = 80%, and taking into account 15% loss to follow-up, this resulted in 99 patients per condition (total n = 198).

A post-calculation was performed mid-trial for detecting a relevant difference within the patient-subgroup receiving step-2 treatment. As our step-2 treatment is comparable with treatment in an earlier study, the effect size of $d = 0{\cdot}62$ on the TQ in that study was used to compute power for our step-2 (Kroner-Herwig, et al., 2003). Given $\alpha = 0{\cdot}05$ (2-sided) and power = 80%, n=41 patients per condition were needed in the 2nd step of care. Assuming that 21% of all patients entering step-1 would enter the step-2, and taking into account 15% attrition, n=232 patients were needed per condition in step-1 (total n = 464). The increment in inclusion was approved by the Medical Ethical Board (METC-SRL: 08/07/2008) and the steering committee of the funding party (ZonMW).

Statistical analysis

The Consolidated Standards of Reporting Trials (CONSORT) was employed to report results (Hopewell, et al., 2008). All statistical analysis were performed with PASW SPSS statistical software version 18·0 (SPSS, 2009).

PROTOCOL-ADHERENCE AND CONTAMINATION CHECK

Protocol-adherence was assessed by dividing the number of required observed elements (essential and unique and essential but not unique), by the maximum possible number of these elements. Treatment contamination was assessed by dividing the number of observed not allowed treatment-elements by the maximum number of these elements (Leeuw, et al., 2009). To check for equality of adherence and contamination scores for both UC and SC over rated treatment-charts an analysis of variance was carried out (for specifics see appendix B).

TREATMENT OUTCOME: INTENTION-TO-TREAT ANALYSES

Intention-to-treat analyses were employed; all patients who were measured at baseline and allocated to treatment were included, irrespective of their participation in subsequent treatment or follow-up measurements. Mixed (multilevel) regression analyses were carried out on all available data per outcome, without imputation of missing data, using treatment, time and covariates as predictors. Details of the mixed model are found in appendix A.

MODERATION OF TINNITUS-SEVERITY

To check whether the difference between SC and UC treatment, as measured with the HUI (health-related quality of life) and the HADS (general negative affect), was different for patients suffering severely from the tinnitus (TQ) and entering step-2, than for those who were only mildly affected receiving step-1 care only, the interaction between tinnitus-severity at baseline and treatment was tested ($\alpha = \cdot01$ for the interaction test with respect to these outcome parameters).

Role of funding source

The funding party was not involved in study design, data collection, data analysis, data interpretation or the preparation of the report. Participation of RFFC, IM, MJ, LA and JWSV was supported by the ZonMw Grant, number: 945-07-715, and all had access to the data. All authors commented on drafts and approved the final report. RFFC had final responsibility for the decision to submit the paper for publication. There were no conflicts of interest.

Results

Flow of participants

Figure 2 shows the flow of participants, including drop-outs, non-responders, reasons for non-response for measurements at one of the follow-ups, and reasons for drop-out if known. Non-response was defined as: measurements were missed at one or more of the follow-ups, nonetheless participants remained in the trial; drop-out was defined as: participants left the trial permanently and told us so.

Of the 741 participants screened for eligibility, 626 were invited for participation, and 492 completed baseline measurements and were randomized to step-1 treatment; of which 247 were allocated to UC, and 245 to SC treatment. Randomization and allocation took place from September 2007 until December 2009. Follow-up measurements were completed in January 2011.

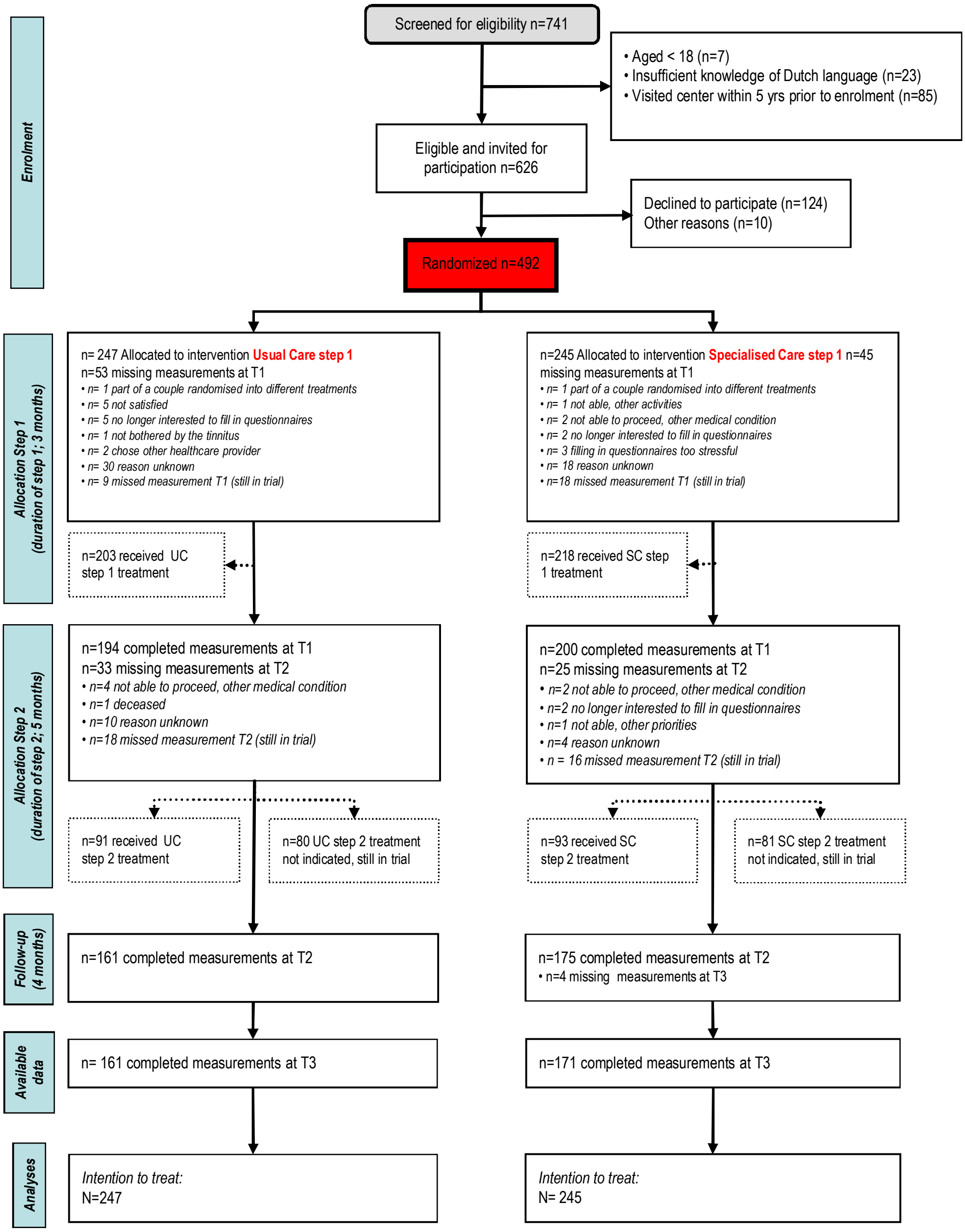
Non-response and drop-out rates per time point did not differ between groups ($\alpha = \cdot01$, $p > \cdot20$), as measured with logistic regression, using missingness (whether due to non-response or dropout) as outcome (0=not missing, 1=missing), and group, baseline covariates (age, gender, education, duration of complaints, tinnitus-severity at baseline and hearing loss) and scores on the HUI, the TQ and the THI on the previous time-point as predictors. Only age was predictive for missingness, with increasing age giving more missingness ($p < \cdot 01$ for age at time points 1 and 2, $p > \cdot 083$ for all other predictors and time points). All baseline covariates were included into all outcome analyses.

From randomization to final follow-up, a loss to follow-up was observed of 34·8% and 30·2% in the UC and SC group respectively. The reasons for non-response seem not to be related to treatment content. The baseline values for all variables, tinnitus characteristics, and audiological data for the total sample, and for UC and SC separately, are displayed in table 1.

Protocol-adherence and contamination check

Interrater-reliability between both raters for the identification of treatment-condition was excellent (Cohen's kappa = ·96), and good for the identification of step-2 treatment and for specific treatments-elements (Cohen's kappa = ·79, and ·74 respectively). Analysis of variance indicated no significant differences between treatment-conditions in protocol-adherence and contamination ($P > \cdot 60$), using the mean scores of adherence and contamination over all rated CRF's.

In 97% of the cases correct classification of treatment-condition of the observed elements occurred (0 = UC, 1= SC), supporting sufficient differentiation between treatment-conditions. On average 87·5% of essential treatment-elements (unique and not unique) occurred during the delivery of both treatments (0 = 'did not occur', 1 = 'did occur') (Mean = 88·4%, SD = 9·02 for UC, and Mean = 87·5%, SD = 12·6 for SC), indicating satisfactory protocol-adherence. On average 6% (Mean = 4·6% and SD = 2·6 for UC, and Mean = 8·1%, SD = 6·1 for SC) of the prohibited treatment-elements occurred during treatment delivery, demonstrating absence of contamination.



UC=Usual Care, SC=Specialized Care, T0 = Month 0, T1 = Month 3, T2 = Month 8, T3 = Month 12

FIGURE 2L CONSORT TRIAL PROFILE

TABLE 1. SUMMARY OF DEMOGRAPHICS, BASELINE MEAN VALUES ON PRIMARY AND SECONDARY OUTCOME MEASURES, TINNITUS CHARACTERISTICS, AND AUDIOMETRIC DATA OF THE ALL PARTICIPANTS, AND EACH GROUP SEPARATELY

	Total (n = 492)		UC (n = 247)		SC (n = 245)	
Age in yrs (SD)	54·2	(11·54)	54·6	(12·02)	53·7	(11·05)
Gender (% male)		62·6		60·7		64·6
Education (%)						
Low		45·7		47·3		44·0
Middle		27·7		24·5		30·9
High		26·6		28·2		25·1
Employment (% yes)		53·4		50·2		56·6
Duration (%)						
less than 1 yr		29·9		32·7		27·2
1 to 5 yrs		38·9		37·9		39·9
more than 5 yrs		31·1		29·4		32·9
Mild complaints TQ < 47 (%)		45·5		45·3		45·7
Tinnitus sound: pure tone (%)		14·5		9·9		17·8
Tinnitus left (ear/head) (%)		25·0		24·8		25,2
Tinnitus right (ear/head) (%)		19·9		19·6		20·1
Continuous tinnitus (%)		83·9		83·3		84·5
Interval tinnitus (%)		6·9		3·0		10·7
Fitting of hearing aid (% yes)		18·5		18·2		18·6
Fitting of sound generator (% yes)		18·9		18·6		19·2
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*
PTA right ear	29·74	19·40	30·30	20·58	29·18	18·15
PTA left ear	31·05	20·64	30·96	20·25	31·14	21·06
PTA bilateral	30·57	17·60	30·77	17·85	30·37	17·38
TQ	49·05	18·85	48·78	19·23	49·32	18·49
TCS	21·11	12·19	21·36	12·57	20·86	11·81
FTQ	7·25	3·59	7·31	3·65	7·19	3·54
THI	38·96	22·88	38·65	23·19	39·27	22·60
HUI	0·635	0·29	0·641	0·30	0·63	0·28
HADS	12·20	8·04	11·79	8·03	12·60	8·05

UC = Usual Care, SC = Specialized Care, SD = Standard Deviation, PTA = Pure tone average for 1, 2 and 4 kHz, TQ =Tinnitus questionnaire, TCS = Tinnitus catastrophizing scale, FTQ = Fear of tinnitus Questionnaire, THI = Tinnitus handicap inventory, HUI = Health utilities index, HADS = Hospital anxiety and depression inventory

Treatment outcome: Intention-to-treat analyses

Significant group differences were found on all outcomes (See table 2 and 3, and figure 3). Group differences favouring SC in health-related quality of life (HUI) were significant at the second and third follow-up (p < ·05 and p < ·01 respectively). Differences in favour of SC with respect to tinnitus-severity (TQ) and tinnitus-related impairment (THI) were found on all 3 follow-ups (p < ·01 at follow-up 1, and p < ·001 at follow-up 2 and 3). Groups also differed, favouring SC, in negative affect (HADS) at the last two follow-ups (p < ·001 at follow-up 2, and p < ·01 at follow-up 3), and in tinnitus catastrophizing (TCS) and tinnitus-related fear (FTQ) on all three follow-ups (p < ·01 at follow-up 1, p < ·001 at follow-up 2 and 3).

Results indicate that the difference between SC and UC was equal at follow-ups 2 and 3, and larger than at follow-up 1. This simplified treatment-effect pattern was tested against the general model as follows): the terms group*t1, group*t2, group*t3 were replaced with a single term group*time, with time coded as 0,0,1,1 for the HUI and 0,1,2,2 for all other outcomes. For all six outcomes, the simplified treatment-effect pattern was supported (p > .05 for the Likelihood Ratio test with *df*=2), indicating that the outcome difference between SC and UC increased from baseline to month 8 and remained stable from month 8 to 12.

Moderation of Tinnitus-severity on treatment effect

No significant interaction effect of tinnitus-severity and treatment on the HUI or the HADS was found at any of the time-points (d.f. = 3, p = ·26 and d.f. = 3, p = ·33 respectively), indicating that the difference between treatment-groups as measured with the HUI or the HADS did not depend on the level of tinnitus-severity as measured with the TQ.

TABLE 2. OBSERVED MEANS AND STANDARD DEVIATIONS (SD) BASED ON ALL AVAILABLE DATA FOR THE OUTCOMES AT BASELINE, FOLLOW UP 1 (AFTER STEP 1, 3 MONTHS AFTER BASELINE), FOLLOW UP 2 (AFTER STEP 2, 8 MONTHS AFTER BASELINE) AND FOLLOW UP 3 (4 MONTHS FOLLOW UP, 12 MONTHS AFTER BASELINE)

Primary outcomes	Baseline UC (n=247) Baseline SC (n=245)		Follow up 1 UC (n=194) Follow up 1 SC (n=200)		Follow up 2 UC (n=161) Follow up 2 SC (n=175)		Follow up 3 UC (n=161) Follow up 3 SC (n=171)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Health related QoL (HUI)								
UC	0·641	0·295	0·640	0·294	0·634	0·287	0·631	0·279
SC	0·628	0·284	0·620	0·285	0·656	0·254	0·681	0·250
Tinnitus Severity (TQ)								
UC	48·87	19·22	45·51	19·65	42·36	19·62	42·12	19·81
SC	49·39	18·50	42·01	19·81	36·47	17·48	33·43	16·89
Tinnitus impairment (THI)								
UC	38·73	23·20	37·38	23·74	34·14	24·60	33·51	23·25
SC	39·25	22·65	34·25	23·44	28·85	20·51	26·45	18·81
Secondary outcomes	Baseline UC (n=247) Baseline SC (n=245)		Follow up 1 UC (n=194) Follow up 1 SC (n=200)		Follow up 2 UC (n=161) Follow up 2 SC (n=175)		Follow up 3 UC (n=161) Follow up 3 SC (n=171)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Negative affect (HADS)								
UC	11·83	8·03	12·08	8·75	11·47	8·55	10·83	8·03
SC	12·61	8·07	11·91	7·96	10·52	7·21	10·22	7·01
Tinnitus catastrophising (TCS)								
UC	21·42	12·56	18·65	11·76	17·14	11·54	15·95	11·79
SC	20·89	11·83	16·20	11·65	12·45	10·30	11·73	9·91
Tinnitus related fear (FTQ)								
UC	7·32	3·66	6·60	3·70	6·19	4·06	6·04	4·00
SC	7·19	3·54	5·60	3·87	4·52	3·50	4·20	3·16

QoL = Quality of life, UC = Usual Care, SC = Specialized Care, SD = Standard Deviation, HUI = Health utilities index, TQ =Tinnitus questionnaire, THI = Tinnitus handicap inventory, HADS = Hospital anxiety and depression inventory, TCS = Tinnitus catastrophizing scale, FTQ = Fear of tinnitus Questionnaire

TABLE 3. ESTIMATED GROUP DIFFERENCE (B) AND 95% CONFIDENCE INTERVALS (C.I.) ON PRIMARY AND SECONDARY OUTCOMES AT FOLLOW UP 1 (3 MONTHS), FOLLOW UP 2 (8 MONTHS), AND FOLLOW UP 3 (12 MONTHS), BASED ON INTENTION TO TREAT ANALYSIS

Primary outcomes	B [1]	95% C.I.		P	E.S. [2]
Health related QoL (HUI)[a]					
3 months	-0·01	0·06	0·04	·642	0·04
8 months	0·04	0·01	0·07	·026	0·18
12 months	0·06	0·03	0·09	·001	0·24
Tinnitus Severity (TQ)[b]					
3 months	-3·31	-5·61	-1·02	·005	0·20
8 months	-7·07	-9·56	-4·58	·000	0·41
12 months	-8·06	-10·83	-5·30	·000	0·43
Tinnitus impairment (THI)[c]					
3 months	-4·26	-7·07	-1·45	·003	0·32
8 months	-7·63	-10·71	-4·54	·000	0·52
12 months	-7·51	-10·66	-4·35	·000	0·45
Secondary outcomes	B	99% C.I.		P	E.S.
Negative affect (HADS)[d]					
3 months	-0·86	-2·18	0·47	·094	0·15
8 months	-2·09	-3·51	-0·66	·000	0·35
12 months	-1·51	-2·87	-0·15	·004	0·24
Tinnitus catastrophising (TCS)[e]					
3 months	-2·10	-3·96	-0·25	·004	0·31
8 months	-4·68	-6·94	-2·43	·000	0·60
12 months	-3·83	-6·19	-1·48	·000	0·41
Tinnitus related fear (FTQ)[f]					
3 months	-0·79	-1·49	-0·08	·004	0·35
8 months	-1·55	-2·35	-0·75	·000	0·58
12 months	-1·50	-2·32	-0·69	·000	0·48

QoL = Quality of life, UC = Usual Care, SC = Specialized Care, SD = Standard Deviation, HUI = Health utilities index, TQ =Tinnitus questionnaire, THI = Tinnitus handicap inventory, HADS = Hospital anxiety and depression inventory, TCS = Tinnitus catastrophizing scale, FTQ = Fear of tinnitus Questionnaire. [1] Since UC is coded as 0 and SC as 1, a negative B shows lower scores in UC than SC at the follow up measurements. The B's displayed are the group * time effects as shown in appendix B, where time = 0 for baseline· time = 1 for follow up 1, time = 2 for follow up 2, and time = 3 for follow up 3; [2] E.S. = Effect size, calculated by dividing the B's (ignoring their sign) by the square root of the average of residual variances at follow up 1, 2 and 3, giving a mixed regression version of Cohen's d. Given in absolute values. [a] Adjusted for the main effects of both stratifiers(hearing loss and tinnitus severity at baseline), and of time (using dummy coding with baseline as reference category); [b] Adjusted for the main effects of education, hearing loss, and time; [c] Adjusted for the main effects of age, duration, education, tinnitus severity at baseline and time, and for interaction effects of time by education and by tinnitus severity at baseline; [d] Adjusted for the main effects of duration, both stratifiers, time, and for interaction effects of time by duration and by tinnitus severity at baseline; [e] Adjusted for the main effects of education, tinnitus severity at baseline, time, and for the interaction effects of time by education and by tinnitus severity at baseline; [f] Adjusted for the main effects tinnitus severity at baseline, time, ,and for the interaction effects of time by tinnitus severity at baseline

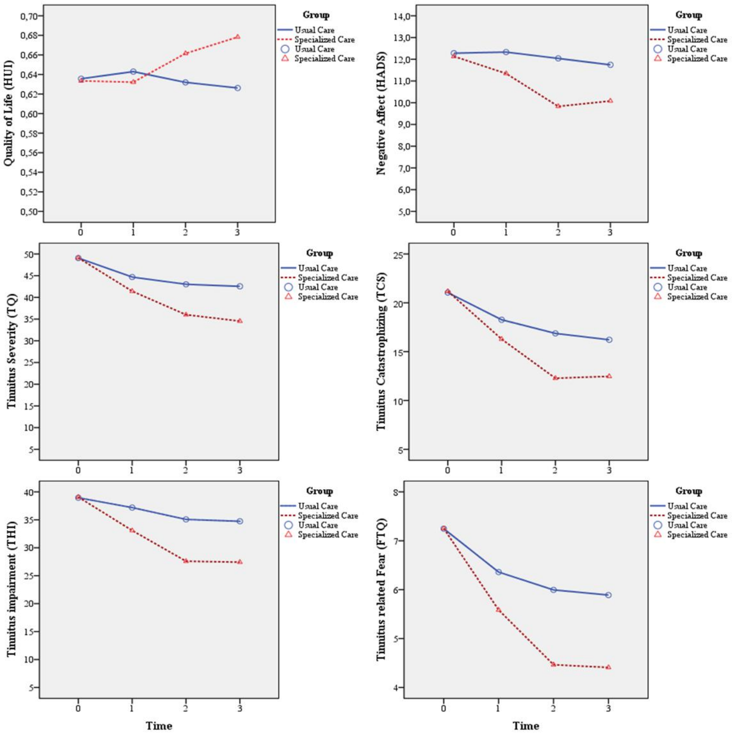


FIGURE 3. GRAPHS DEPICTING THE CHANGE OVER TIME IN PRIMARY AND SECONDARY OUTCOMES FOR BOTH USUAL CARE AND SPECIALIZED CARE; USING PREDICTED VALUES FROM THE FINAL GENERAL MODELS

Discussion

This study demonstrates that stepped-care tinnitus management, combining elements of TRT within a CBT-framework (SC), is more effective than usual care (UC) in increasing health-related quality of life, and reducing tinnitus-severity and tinnitus impairment. Additionally, SC compared to UC generates greater improvements in general negative emotional states, level of tinnitus-related catastrophic thinking and tinnitus-related fear. The effectiveness of SC as compared to UC has been demonstrated not only after the first 3 months of step-1 treatment, but also after the more intensive step-2 treatment approach, as well as after 4 months of no-treatment. Results are even more striking in that patients with mild tinnitus complaints, receiving step-1 treatment only, were included in all analyses.

Furthermore, mild and severe tinnitus sufferers, as measured with the Tinnitus Questionnaire at baseline, appeared to benefit equally from getting SC treatment instead of UC treatment. These findings support our main hypothesis that a CBT based stepped care approach with elements from TRT, is effective in tinnitus management, both for milder forms of tinnitus suffering as well as for more severe tinnitus incapacitation.

Two main treatment-approaches have dominated the management of patients with tinnitus complaints. The TRT approach, with a focus on sound habituation, as well as the CBT approach, with a focus on dysfunctional beliefs about tinnitus and associated safety behaviours, have been widely applied and studied (Hesser, et al., 2011; Hoare, et al., 2010; Martinez Devesa, et al., 2007; Phillips & McFerran, 2010). However, a combination of the two, though previously proposed (Cima, Crombez, et al., 2011; Seydel, Haupt, Szczepek, Klapp, & Mazurek, 2010), has never before been investigated in a randomized controlled trial of this scale.

Particular strengths of our study are a relatively large sample size, the blinding of assessors, the assessment of treatment fidelity strengthening internal validity, and the delivery of the treatments according to protocols. Other strengths are the zero dropouts from step-2 treatment, the fact that both generic and tinnitus-specific outcome measures reveal consistent findings, and moreover, the differences between UC and SC treatment over time are likely to be clinically relevant. The percentage of patients reporting clinically relevant changes (Rief, et al., 2005; Samsa, et al., 1999) after 12 months in health-related quality of life and in tinnitus-severity was larger in the SC group.

There are also some limitations. *First*, our specialized care treatment consisted of several elements, and it is unclear which of those contributed to the overall effectiveness. Future studies might adopt a dismantling approach, leaving out potentially redundant treatment components in subsequent trials. *Second*, the treatment was carried out in an outpatient clinic for audiological rehabilitation. The question remains whether our results can be generalized to other health-care settings, where generalisability is dependent on their similarity to the present setting. We are currently investigating implementation routes in both primary and secondary care.

Next to the analyses reported presently, *first,* moderation and mediation analyses are being carried out, providing additional information about underlying mechanisms of change, contributing to further refinement, tailoring, and increased effectiveness of the treatment. *Second*, cost-effectiveness data of SC compared to UC are not included currently, but are planned to be reported separately. *Third,* data was gathered using a seventh measure, the Tinnitus Coping and Cognitions List (TCCL). The main reason for including this measure was to test the psychometric properties of this new measure in patients with tinnitus. The TCCL has considerable content overlap with the TCS, therefore by omitting the TCCL from effect-analyses, crucial information is not missed currently and psychometric analysis is planned to be reported separately.

In conclusion, our findings provide firm evidence for an effective new treatment-approach in tinnitus-management. Results are highly relevant for clinical practice, given that best-practice for tinnitus has not been defined yet (Hoare, et al., 2012), leading to fragmentized costly treatment-trajectories (Cima, et al., 2009). Delay of psycho-education and effective treatment is expected to aggravate tinnitus-complaints, increasing psychological strain and unnecessary prolongation of suffering. Current findings could lead to consensus in policy about best-practice in tinnitus-treatment, standard choices in referral-trajectories and the implementation of standardized tinnitus assessment and thereby comparable outcomes.

Contributors

The trial project members RFFC (principal investigator and main author), MAJ (project advisor and co-promotor), LJCA (project co-leader), and JWSV (project leader) designed the study and obtained funding. RFFC and DJWMS (project member and clinical audiology advisor) carried out the literature search for the systematic review and carried out the qualitative study for the development of the protocol of usual care. RFFC and DJWM, in close collaboration with the specialised care professionals of Adelante; Audiology and Communication, developed the specialised care protocol. Treatment manuals of Usual Care and Specialised Care were developed by RFFC and DJWMS, and MAJ and LJCA commented on drafts of the manuals. Further trial development and design was carried out by the trial management group RFFC, MAJ, LJCA, JWSV, and IHM (principal investigator economic evaluation). Supporting literature searches were carried out by all members of the trial management group. Data collection was carried out by RFFC and IHM; they monitored data collection and integrity of randomization. The statistical analysis plan was set up by RFFC, JWSV, and GJPB (advisor statistical analyses). The statistical analyses were carried out by RFFC, supported by GJPB. Data interpretation was carried out by RFFC and GJPB. Trial treatments and the UC and SC treatment teams were coordinated and monitored by RFFC. RFFC, JWSV, and GJBP were involved in the writing of the current manuscript, the design of tables, figures, appendices and panels. RFFC was responsible for writing and for the decision to submit the final paper for publication. All co-authors commented on drafts of the manuscript and approved the final report.

Conflicts of interest:

All authors declare to have no conflicts of interest.

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APPENDIX A: The mixed model for testing treatment effects on outcomes

Due to the randomization, pre-stratified on hearing loss and tinnitus severity, no significant baseline differences were expected between treatment conditions. However age, gender, education, hearing loss and tinnitus severity were included as covariates as to improve power. Since duration of complaints was a potentially relevant prognostic variable, this was added to the model as well[1]. The repeated measures per outcome were checked for multivariate outliers (mahalanobis distance, $p < \cdot 001$), and no such outliers were found for any outcome. Collinearity between covariates was checked but not found either, as all covariates had a variance inflation factor (VIF) below 1·5.

Since there were 4 repeated measures, time was entered in the mixed regression as a categorical variable using dummy coding[2], with the baseline as a reference category and a dummy indicator for every other time point (giving three dummies), to assess group differences in change from baseline, allowing for possible nonlinear change. To correct for multiple testing $\alpha = \cdot 05$ and $\alpha = \cdot 01$ (two-tailed) were used for primary and secondary outcomes, respectively.

The initial model included group, time, covariates, group by time, and covariate by time effects[3]. Each model change was tested for significance using Maximum Likelihood (ML) estimation and a likelihood ratio test with 'k' degrees of freedom (k = the difference in number of parameters between two successive models).

To enhance parsimony and increase interpretability of the model the following modelling steps were taken. First, every non-significant covariate by time interaction was removed, treating terms concerning the same predictor as one block with *d.f.* = 3 (e.g. *cov * followup1*, *cov* followup2*, and *cov * followup3* in the panel below). Second, covariates that were neither significant nor involved in a covariate * time term, were stepwise removed with *d.f.* = 1, again using the same restrictive α's. Third, the 'main' group effect (β_1 in the equation) was dropped from the model, which is a valid and power-improving step in randomized trials.[1, 2]

Since baseline is the reference point, the 'main 'effect of 'group' actually reflects the group difference at baseline (see panel below). This effect is zero apart from sampling error due to randomization. The final mixed model per outcome was re-run with the restricted maximum likelihood method (REML) instead of ML to obtain better estimates of the standard errors. [3]

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[1] Categorical covariates were entered in the model using dummy coding, for Gender: 0 = male, 1 = female; Education dummy 1: 0 = low, 1 = middle, 0 = high; education dummy 2: 0 = low, 0 = middle, 1 = high. Each quantitative covariate was centred (Cov – sample mean = CovCen) and its quadratic form (CovCen * CovCen = CovCen2) was added to the model to assess possible nonlinear effects of the covariates on the outcomes.

[2] For each time point except baseline (the reference category) a dummy indicator was entered in the model.

[3] Prior to the initial models we tested each covariate by treatment interaction over time with a separate mixed regression model per covariate, with three way interactions of group, covariate and time and all corresponding lower order terms. No such three way interactions were found.

The mixed model equation for testing treatment effects on outcomes

y_{ti} = $\beta_0 + \beta_1\,\text{group} + \beta_2\,\text{cov} + \beta_3\,\text{followup1} + \beta_4\,\text{followup2} + \beta_5\,\text{followup3} + \beta_6\,\text{group x followup1} + \beta_7\,\text{group x followup2} + \beta_8\,\text{group x followup3} + \beta_9\,\text{cov x followup1} + \beta_{10}\,\text{cov x followup2} + \beta_{11}\,\text{cov x followup3} + e_{ti}$

Where:

t = Time

i = Patient identifier

group = 0 for patients assigned to UC and 1 for patients assigned to SC

cov = The covariates: hearing level and tinnitus severity at baseline, age, gender, education, duration of complaints (see table 4) (the actual model contained multiple covariates and covariate by time effects)

followup1 = 1 if t = 1 and 0 if else (see footnote 2 in section statistical analysis, treatment outcome), and likewise for followup2 (=1 if t=2 and 0 else) and followup 3 (= 1 if t=3 and 0 else)

e_{ti} = The random effect of patient i at time point t

With the following interpretation:

β_0 = The mean baseline in group 0 (UC)

β_1 = The mean baseline difference between groups (SC-UC) , expected to be zero due to the randomisation

β_2 = The association between the specific covariate and the outcome at baseline

β_3 = The mean change from baseline to follow up 1 (3 months after baseline) within patients who score 0 on all predictors included in the final model (e.g. group = UC, Gender = male, mean score on covariates), and likewise for β_4 (change from baseline to follow up 2) and β_5 (change from baseline to follow up 3)

β_6 = The group difference (SC-UC) in mean change from baseline to follow up 1 (3 months after baseline), which is also the group difference at follow up 1 since there is no difference at baseline, and likewise for β_7 (group difference in change from baseline to follow up 2) and β_8 (group difference in change from baseline to follow up 3)

β_9 = The effect of a specific covariate on the change from baseline to follow up 1 in both treatment conditions, and likewise for β_{10} (covariate effect on change from baseline to follow up 2) and β_{11} (covariate effect on change from baseline to follow up 3)

The covariate * time interactions were dropped from the model if not significant, as assessed by a likelihood ratio test.

The null hypothesis of no difference between UC and SC implies that $\beta_6 = \beta_7 = \beta_8 = 0$.. This null hypothesis was tested against the alternative of a difference between treatments at follow up 1, 2, and 3, with a likelihood test, df = 3

The null hypothesis of no difference between UC and SC at time point 1, follow up 1, and an equal difference at time points 2 and 3, follow up 2, and follow up 3, implies that $\beta_6 = 0$; and $\beta_7 = \beta_8 \neq 0$. This hypothesis was tested against the general model, with a likelihood ratio test, df = 2

The null hypothesis of linear increase in difference at the first 2 time points, follow up 1, and follow up 2, and an equal difference at follow up 3, implies that $2\beta_6 = \beta_7 = \beta_8 \neq 0$. This hypothesis was tested against the general model, with a likelihood ratio test, df = 2

The 4 random effects (e_{1i}, e_{2i}, e_{3i}, e_{4i}) were assumed to be multivariate normally distributed with an unspecified covariance matrix, which is the most general covariance structure.

APPENDIX B: Specifics on data collection

Data collection for treatment Effects:

Baseline measurements were completed at the off-centre site, where respondents were assisted by one of four research assistants in using an internet-based environment. Two weeks prior to follow up 1 (3 months after baseline), follow up 2 (8 months after baseline), and follow up 3 (12 months after baseline), personal log-in codes were sent by postal mail to every participant, enabling test-completion online. If participants were not able to use the online system, either a paper version was sent to them by postal mail, or they were invited to the centre to receive help from a research assistant.

Data collection for treatment fidelity check:

A trial-specific measure was developed[1] enabling 2 independent assessors to rate whether specific treatment-elements took place or not, without revealing whether or not these were required, allowed or prohibited and to assess the rater's judgement which treatment-condition the treatment-elements belonged to, and if Step-2 treatment was delivered. First, specific treatment-elements were listed by 2 experts of both treatment-protocols. Second, these experts categorized these elements into 5 categories; 1) Essential and unique, 2) Essential but not unique, 3) Unique but not essential, 4) Compatible, and 5) Prohibited. The content validity of this measure was supported by sufficient independent agreement (kappa = ·83) between the two experts in categorizing all identified elements. Independent raters, both postgraduates in psychology, not involved in treatment, and not affiliated with the centre, rated a random sample of 40 CRF's per treatment-condition and crosschecked occurrence of elements, using this measure. Imperative before treatment fidelity analysis were the following criteria: First, sufficient interrater reliability of the trial specific fidelity check instrument had to be established between the two independent raters (Cohen's Kappa > ·70). Second, sufficient protocol-adherence requires that at least 70% of essential treatment-elements have actually occurred (essential and unique, and essential but not unique). Third, contamination can be considered ignorable when no more than 10% of prohibited treatment-elements occur.

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CHAPTER VII

COST-EFFECTIVENESS OF SPECIALIZED TREATMENT BASED ON COGNITIVE BEHAVIORAL THERAPY VERSUS USUAL CARE FOR TINNITUS

Submitted as

Maes, I.H.L., Cima, R.F.F., Anteunis, L.J.C., Scheijen, D.J.W.M., Baguley, D.M., El Refaie, A., Vlaeyen, J.W.S., Joore, M.A. (2013). Cost-effectiveness of specialized treatment based on cognitive behavioral therapy versus usual care for tinnitus.

Abstract

Objective: Up to 21% of adults will develop tinnitus, manifesting the perception of a noxious disabling internal sound. Many different treatments are offered, but evidence on their effectiveness and cost-effectiveness is scarce or absent. Recently, the effectiveness of a specialised treatment of tinnitus based on cognitive behavioural therapy was demonstrated. The present study evaluates the cost-effectiveness of this treatment compared to care as usual, in an audiological centre.

Methods: An economic evaluation was carried out alongside a randomized controlled clinical trial. The economic evaluation was conducted from a societal perspective, using a one-year time horizon. The incremental cost effectiveness ratio (ICER) was calculated by dividing the difference in costs by the difference in Quality Adjusted Life Years (QALYs) based on the HUI Mark III. Non-parametric bootstrapping and sensitivity analyses were used to assess uncertainty in costs and effects. Sensitivity analysis included a complete cases analysis and analysis on data were missing values on the HUI mark III were imputed based on a mixed regression model from the clinical effectiveness analysis.

Results: Compared to patients receiving usual care, patients who received specialised care gained on average 0.015 QALYs (BCI:-0.028-0.055). The incremental costs from a societal perspective are €286(95% BCI:- €828 - €1,427). The incremental cost per QALY from a societal perspective amounted to €19,688. The probability that SC is cost-effective from a societal perspective is 58% for a willingness to pay for a QALY of €36,000.

Conclusion: Specialised multidisciplinary tinnitus based on cognitive behavioural therapy may be cost-effective as compared to usual care.

Keywords: tinnitus, cognitive behavioral therapy, cost-effectiveness, multidisciplinary treatment

Introduction

Tinnitus is the perception of a pernicious, and for some disabling sound for which there is no acoustic source. The prevalence of tinnitus in the western world is between 10-20% (Andersson, 2002; Davis & El Refaie, 2000) and approximately 3-5% of the general population is severely impaired by the tinnitus (Davis & El Refaie, 2000; Vesterager, 1997). There are several theories on the potential mechanisms that underlie tinnitus but none of these have been demonstrated scientifically (Henry, Dennis, & Schechter, 2005). As a result there is no known drug or curative therapy at present (Ahmad & Seidman, 2004; Andersson, Baguley, McKenna, & McFerran, 2005) and tinnitus care is often fragmentized and costly (Lockwood, Salvi, & Burkard, 2002).

Tinnitus is known to cause affective problems, sleep difficulties and major impact upon concentration (Bartels, Middel, van der Laan, Staal, & Albers, 2008; Davis & El Refaie, 2000; Henry, et al., 2005). The combination of these complaints makes tinnitus sufferers feel exhausted and frustrated, resulting in diminished quality of life for the sufferers and sometimes their extended family (El Refaie, et al., 2004; Erlandsson & Hallberg, 2000; Jastreboff, Gray, & Gold, 1996; Kroner-Herwig, Frenzel, Fritsche, Schilkowsky, & Esser, 2003; Scott, Lindberg, Melin, & Lyttkens, 1990). Therefore, almost all therapies are focused on alleviating tinnitus related distress and improving quality of life (Henry, et al., 2005).

The most frequent used approaches in relieving tinnitus distress and improving quality of life involve counseling, and hearing aid fitting to compensate hearing loss or provide sound generators or tinnitus maskers, but there is mixed evidence to support their clinical effectiveness (Hoare, Gander, Collins, Smith, & Hall, 2010; Hobson, Chisholm, & El Refaie). Evidence regarding the efficacy of clinical interventions remains sparse, but there are indications of benefit from Tinnitus Retraining Therapy (Forti, et al., 2009; Henry, et al., 2007; Henry, Schechter, Nagler, & Fausti, 2002; Herraiz, Hernandez, Toledano, & Aparicio, 2007; Phillips & McFerran, 2010), Cognitive Behavioral Therapy (El Refaie, et al., 2004; Gudex, Skellgaard, West, & Sorensen, 2009; Hesser, Weise, Westin, & Andersson, 2011; Martinez Devesa, Waddell, Perera, & Theodoulou, 2007) and a combination of therapies (Hoare, et al., 2010). Tinnitus Retraining Therapy (TRT) is based on the neurophysiologic model of tinnitus developed by Jastreboff (Jastreboff, et al., 1996). TRT involves [1] extensive directive counseling about tinnitus to reduce aversive reactions to the symptom and [2] sound therapy to facilitate habituation to the tinnitus signal (Jastreboff, et al., 1996).

Cognitive behavioral therapy is used to alter psychological processes that are considered to maintain or contribute to tinnitus-related complaints. Treatments that combine counseling and a listening device are also effective (El Refaie, et al., 2004; Gudex, et al., 2009). A study by El Refaie (El Refaie, et al., 2004) even found a significant effect on the SF-6D health state utilities. In the recent literature an integrated approach to treatment that combines insights from audiology, otology, psychology and other disciplines is promoted (Andersson, et al., 2005). Recently, the first convincing results were demonstrated that such a multidisciplinary approach is effective in the treatment of tinnitus (R. F. Cima, et al., 2012; Langguth, 2012). Patients improved in health related quality of life, tinnitus severity and disability due to tinnitus. However, several regulatory authorities also emphasize the impact of assessing the value in health care programs (NICE, 2008; RVZ, 2006), to assess whether health is improved at a reasonable price. This is critically important in a condition like tinnitus since it is known to be costly to people who have it and to society at large.

To our knowledge this is the first study of a multidisciplinary tinnitus treatment that involves a complete health economic evaluation. The objective of this study was to determine the cost-effectiveness of a specialized multidisciplinary tinnitus treatment based on cognitive behavioral therapy, compared to care as usual, in an audiological centre.

Methods

Study Design

An economic evaluation was performed alongside a randomized controlled clinical trial in an audiological centre in the Netherlands (Adelante Audiology and Communication, location Hoensbroek). Patients were allocated to specialized multidisciplinary treatment based on cognitive behavioral therapy, which will be referred to as Specialized Care (SC), or Usual Care (UC), both provided by the audiological centre. Measures were taken for blinding patients to treatment assignment. Follow-up took place at three, eight and twelve months after randomization, with a no-contact period in the last 4 months in the trial. Non responders were monitored and at follow up measurements contacted by telephone and reminded about the follow up, up to two weeks after expiry of the due date. For assessing the cost-effectiveness, the SC group was compared to the UC group. The analyses were performed from a societal perspective, meaning that health care costs, patient and family costs, and productivity losses are included.

Interventions

SC was based on a stepped-care approach, tailored to individual patient needs. The first step of SC consists of a multidisciplinary intervention for all patients, including audiological diagnostics and intervention (counseling, prescription of hearing aid and/or sound generator), a Tinnitus Educational Group session and an individual consult with a psychologist. Based on the scores of the TQ patients were classified into three different severity classes: mild (TQ≤30), moderate (30<TQ<47) or severe (TQ≥47) complaints and severe tinnitus complaints. For patients with mild complaints this basic intervention was expected to be sufficient. For patients with moderate to severe complaints a second step was offered that consists of two main group treatments. Program A for patients suffering from tinnitus on a moderate to severe level consisted of 12 weekly group session. Program B for patients with severe tinnitus complaints consisted of 24 bi-weekly group sessions. Both programs comprise key elements of cognitive-behavioral therapy, education, relaxation techniques, attention diversion, exposure in daily life situations, and tinnitus retraining therapy.

UC consisted of a standardized version of the treatment that is currently applied in audiological centres throughout the Netherlands for tinnitus patients. UC was organized in a stepped care manner and consisted in step 1 of audiological diagnostics and intervention (counseling, prescription of hearing aid and/or sound generator) and, in step 2 if necessary, one or more consultations with a social worker with a maximum of ten one-hour-sessions (See Cima et al., 2009 for more detailed information).

Participants

The study population consisted of tinnitus sufferers referred to the audiological centre, with subjective tinnitus complaints, aged 18 years and older. Patients were excluded from the study if they were not able to read and write in Dutch. Patients who declared in writing to be willing to participate were invited for a first off-centre assessment contact, after which they were allocated to either to UC or SC.

Effects

The primary effect parameter in the economic evaluation is the Quality Adjusted Life Year (QALY). The QALY is based on health state utilities measured with the Health Utilities Index Mark III (HUI). The HUI is a 17 item questionnaire to assess generic health related quality of life on eight dimensions: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain/complaints. Patients with tinnitus especially have complaints in the pain, cognition, emotion and hearing dimension (Maes, Joore, Cima, Vlaeyen, & Anteunis, 2011). A multiplicative utility scoring function was used to determine the utility scores which range from -0.36 to 1.00 (Feeny, et al., 2002). The minimal clinically relevant difference in these utility scores is considered to be 0.03 points (Horsman, Furlong, Feeny, & Torrance, 2003; Marra, et al., 2005). The HUI has shown adequate responsiveness in a tinnitus population (Maes, et al., 2011). The utility scores were used to calculate QALYs using the area under the curve midpoint method:

$$QALY_i = ((U_{i,t0}+U_{i,t1})/2)*T_1(t_1-t_0)+((U_{i,t1}+U_{i,t2})/2)*T_2(t_2-t_1)+((U_{i,t2}+U_{i,t3})/2)*T_3(t_3-t_2)$$

Cost Analysis

Costs in the analysis include health care costs, patient and family costs, and indirect costs. The health care costs consisted of the costs of tinnitus care as provided at the audiological centre, and other health care costs associated with tinnitus. The exact amount of care consumed at the audiological centre by each patient was registered in clinical record forms. The unit costs of a hearing aid were taken from the GIP databank[1] 2009, and the costs of hearing aid fitting were based on information from the Dutch Association of Hearing Aid Dispensers. The unit cost of a tinnitus masking device was determined based on personal communication with several hearing aid dispensers. The unit costs of Treatment Group A and B, Individual Treatment and the Tinnitus

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[1] The GIP databank is an information system of the Health Care Insurance containing information on expenditure on (extramural) drugs and medical aids under the Health Care insurance act.

Educational Group session in SC were determined by a cost calculation. This cost calculation was based on a registration of personnel time and materials used, after which overhead was included. Salary costs for each discipline were based on the average salary per scale (employer's costs included) that are normally used in Dutch audiological centres in 2009. Unit costs of material were market prices from 2009. The depreciation period of the variable material costs was 5 years. The rental of the gym was based on the invoice from the audiological centre of 2009. As recommended (Hakkaart - van Roijen, Tan, & Bouwmans, 2010) an overhead of 35.5% was calculated over the total costs. Prices of individual treatment were calculated based on the number of contacts the patient had with each health care professional. The costs of the Tinnitus Educational Group session were calculated by multiplying the average hourly salary scale of an audiological assistant (€29.55) by 240 minutes (including 120 minutes of group session and 10 minutes indirect time per patient). Total costs of the Tinnitus Educational Group session were €160.16 (including 35.5% overhead costs). Since 12 patients can participate in this group the unit cost per patient is € 13.35. All remaining unit costs of tinnitus care at the audiological centre were based on an anonymous source.[2]

Other health care costs associated with tinnitus included contacts with the general practitioner practice, hospital care, care provided by other health care professionals, and medication. This resource use was measured using a self-administered cost questionnaire with a recall period of three months. The questionnaire was administered at each follow up measurement. The unit costs of the other health care costs were adopted from the Dutch guideline for cost research (Hakkaart - van Roijen, et al., 2010) unless stated otherwise (Table III). The cost questionnaire included items to measure patient and family costs in the three months prior to the follow-up measurement (travel expenses, over the counter medication and other expenses). In the final analysis these costs were interpolated to yearly costs by using the following formula: $Cost_i = C_{i,t1} + (C_{i,t2}/3)*5 + (C_{i,t3})/3)*4$. Also included in the cost questionnaire were the PRODISQ items (Koopmanschap, 2005) to measure loss of productivity (indirect costs). The costs of loss of productivity were quantified using the friction cost method, as recommended in the Netherlands

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[2] In the current Dutch health care system organizations negotiate unit costs of (some of) their products with health care insurance companies. Therefore, some unit costs are business confidential. As a result, it was decided not to reveal the source of unit costs for these care components.

(Hakkaart - van Roijen, et al., 2010). Whenever necessary, unit costs were converted to the reference year 2009 by means of price index figures.

Statistical analysis

Baseline data on utilities and costs were tested for normality with a Kolmogorov-Smirnov test. Differences between the groups on baseline utility scores and costs were compared with an independent samples t-test or a Mann Witney U test, depending on the test for normality. Analyses were performed from both the societal and the health care perspective. First, mean incremental (societal or health care) costs and QALYs per patient between SC and UC were calculated. Incremental cost-utility ratios were calculated by dividing the mean incremental (societal or health care) costs per patient by the mean incremental QALY per patient. In the Netherlands there is no formal threshold for cost-effectiveness therefore a maximum willingness to pay per QALY of £30.000 (approximately €35.000) was used in accordance with the NICE guidelines (Devlin & Parkin, 2004; Raftery, 2001). Incomplete data (missing items) on the HUI mark III were imputed using missing value analysis based on regression in SPSS version 18. Complete missing data on HUI mark III and missing data on the cost questionnaires were calculated using Rubin’s multiple imputation (Rubin, 1987) in SPSS version 18. This method generates 5 different data sets for imputed data. All analyses were performed with each of these 5 data sets and these results were pooled. Uncertainty was characterized using nonparametric bootstrapping with 1,000 simulations in Excel. Confidence intervals for the (incremental) costs and QALYs were calculated from the bootstrap results. Uncertainty of the incremental cost-effectiveness ratio is shown in cost-effectiveness planes. The implications of the uncertainty on decision making (the probability specialized tinnitus care provided in a specialized tinnitus centre is more cost-effective than usual care) is shown in cost-effectiveness acceptability curves for a range of willingness to pay thresholds for a QALY.

Sensitivity analyses

As recommended by Blough et al. (Blough, Ramsey, Sullivan, & Yusen, 2009), sensitivity analyses were used to show the impact of different ways of handling missing values. In the clinical effectiveness analysis of this trial (Cima, et al., 2012) a series of mixed (multilevel) regression analyses were carried out, in which all available data are used without the need for imputation of missing data (Snijders & Bosker, 1999). In one of these analyses, the HUI utility score was used as dependent variable in a repeated measures design with group (US, SC) as the between-subject factor and time (baseline, follow up 1, follow up 2 and follow up 3) as the within-subject factor. Predicted values were calculated from the regression equation of the final model. In the first sensitivity analysis these predicted values were used to impute missing values on the HUI utility scores. The second sensitivity analysis was a complete cases analysis, based on participants for whom both a QALY as well as total societal costs were available.

Results

Participants

Figure 1 shows the flow of participants, including drop-outs, non-responders, as well as reasons for non-response at one of the follow up, or drop-out if known. Randomization and allocation started in September 2007 and ended in December 2009. Follow-up measurements were completed in January 2011. Of the 741 participants who were screened for eligibility, 626 were invited for participation and 492 were randomized to one of the treatment arms. 247 were randomized to UC and 245 to SC. Of the 203 participants that finished the first step of treatment in the UC, a total of 91 patients (46,9%) were identified as having more severe tinnitus complaints and received step 2 UC treatment. Of the 218 patients that finished the first step in SC, a total of 93 patients (46,7%) met criteria for step 2 treatment (TQ score > 47) and were treated. All patients diagnosed as having mild complaints, either in UC (41, 2%) or in SC (40, 7%), remained in the trial for follow up measurements without treatment in the second step. Drop-out and non response rates per time point, and number of patients did not differ between groups ($\alpha = .01$). From randomization to final follow up, a loss to follow up as a result of measurement attrition of 35% in the UC group and in the SC group of 30% was observed. The proportion of missing data and or non-response is acceptable for current analyses. The reasons for non-response seem not to be related to treatment content.

In Table I the sample characteristics for the total group and UC and SC separately are displayed. There were no significant differences found in demographic variables (p >.20). Participants were evenly divided among treatment condition on the basis of hearing loss as well (p =.95).

Effects

Baseline utility scores were not normally distributed (p =.000, K-S test). The baseline utility scores on the HUI mark III were 0.64 (SD = 0.29) in the UC group and 0.63 (SD = 0.28) in the SC group. This difference was not statistically significant (Mann Whitney U Test; p =.503). In terms of effectiveness utility scores increased from 0.63 to 0.65 for the specialized care and decreased from 0.64 to 0.61 for the usual care group (Table II). In both groups the health state utility decreases in the first three months. After this there is a gain in health state utility, as measured with the HUI mark III that continues up to 12 months in the SC while in the UC health related quality of life further decreases (Table II). A clinical relevant decrease on health state utility was measured in the UC care group, while there was no clinical relevant improvement in the SC group based on the base case analysis. In the base case analysis, the incremental QALY is 0.015 (Bootstrapped 95% confidence interval: -0.030 – 0.058). The data in Table II show that the way of handling missing values impacts the utility scores. The predicted values from the multilevel mixed regression and the complete case analysis did indicate a clinically important change in the SC group.

Costs

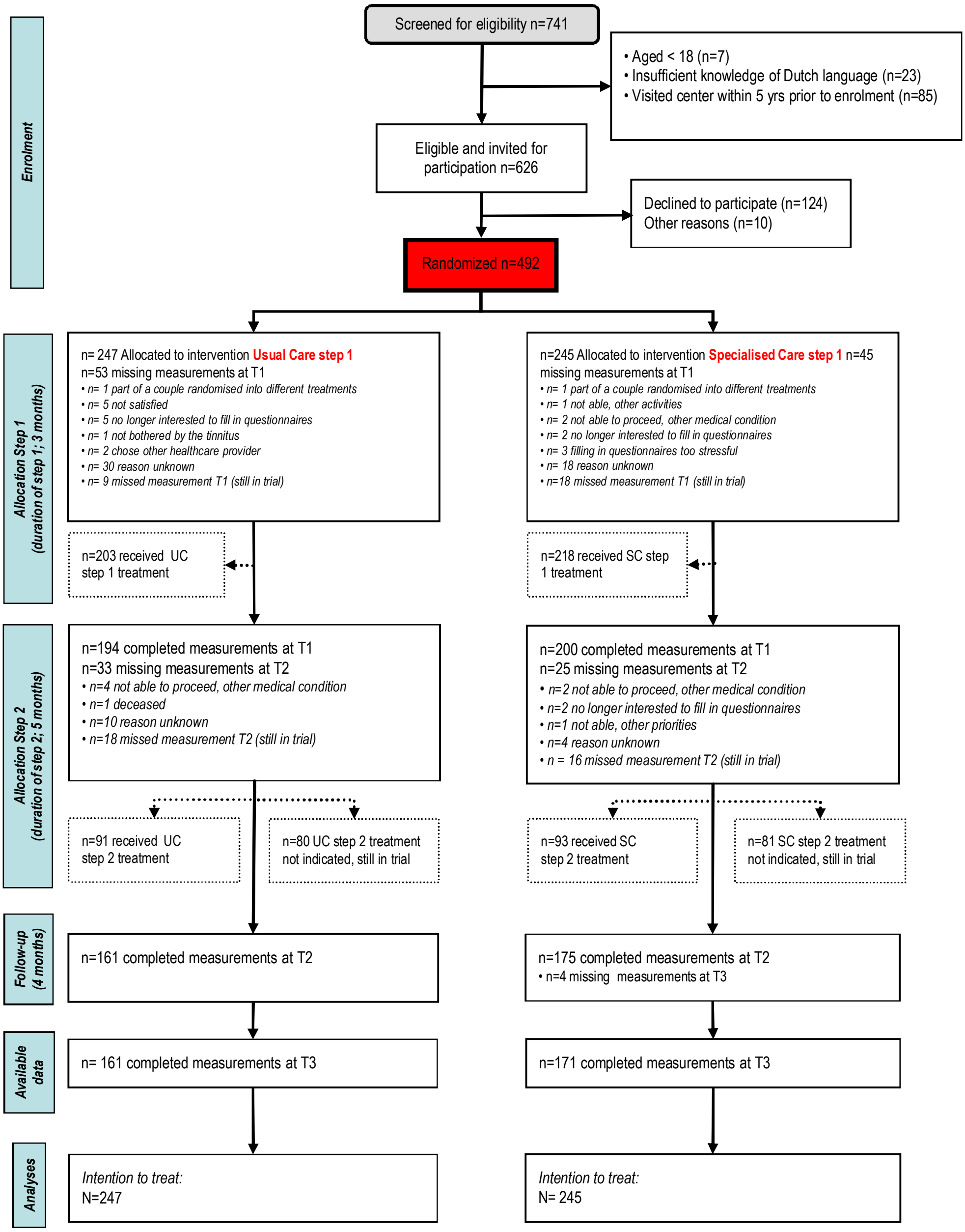
At baseline, costs were not normally distributed (p=.000, K-S test). The total costs from a societal perspective at baseline were €1,480 for UC and €1,322 for SC (Table 1). No significant differences in costs between the groups for one of the cost categories (Mann Whitney U Test; p>.200), or for the total costs were observed (Mann Whitney U Test; p=.828). Table 3 summarizes the number of patients that recorded the use of the different resources at least once during the follow-up period and the mean costs per patient for each group. The mean total health care costs per patient amount to €3,110 in UC and €3,231 in SC. The costs of both first and second level tinnitus care at the audiological centre are higher in SC (€1,675 and €555 respectively) than in UC (€1,480 and €292 respectively). Other health care costs related to tinnitus are lower in SC. The mean total societal costs amount to €5,636 in UC and €5,921 in SC. Patient and family costs are similar in both groups. Costs of lost productivity are higher in SC. In the base case analysis, the incremental costs from a societal perspective are €286 (Bootstrapped 95% confidence interval: -€828 – €1427).

TABLE I. SUMMARY OF DEMOGRAPHIC CHARACTERISTIC, HEARING LOSS AND BASELINE COSTS OF THE ALL PARTICIPANTS AND FOR EACH GROUP SEPARATELY

	Total (n = 492)	UC (n = 247)	SC (n = 245)	p*
Age in yrs (SD)	54,21 (11,52)	54,60 (11,99)	53,82 (11.05)	045
Gender (% male)	62.8	60.7	64.9	0.38
Education (%)				0.39
Low	45.7	47.4	44.1	
Middle	27.4	24.7	30.2	
High	26.8	27.9	25.7	
Employment (% yes)	53.2	50.2	56.1	0.21
Duration (%)				0.26
Less than 1 yr	30.3	33.6	27.0	
1 to 5 yrs	38.7	37.7	39.8	
More than 5 yrs	31.0	28.7	33.2	
Fletcher index (1, 2 and 4 kHZ)	30.8	30.8	30.9	0.95
Costs (societal perspective)	1749	1848	1651	0.20

UC = Usual Care, SC = Specialized Care

*Chi square tests (α= .05) for categorical variables, independent t-tests for continuous outcomes, Mann-Whitney U Test if data were not normally distributed.



UC=Usual Care, SC=Specialized Care, T0 = Month 0, T1 = Month 3, T2 = Month 8, T3 = Month 12

FIGURE 2L CONSORT TRIAL PROFILE

TABLE II. MEAN UTILITY SCORES AND QALYS FOR DIFFERENT WAYS OF HANDLING MISSING DATA.

HUI	Way of handling missing data					
	Multiple Imputation (base case)		Predicted Values from MMR		Complete Cases Analysis	
	UC	SC	UC	SC	UC	SC
N	247	245	247	245	130	140
baseline	0.64 (0.29)	0.63 (0.28)	0.64 (0.29)	0.63 (0.28)	0.64 (0.30)	0.65 (0.26)
3 mo	0.62 (0.31)	0.62 (0.28)	0.63 (0.26)	0.63 (0.25)	0.64 (0.28)	0.64 (0.26)
8 mo	0.62 (0.31)	0.64 (0.29)	0.63 (0.23)	0.66 (0.22)	0.63 (0.28)	0.68 (0.23)
12 mo	0.61 (0.31)	0.65 (0.29)	0.63 (0.23)	0.68 (0.21)	0.63 (0.28)	0.69 (0.24)
QALY	0.62 (0.25)	0.64 (0.22)	0.63 (0.22)	0.65 (0.20)	0.64 (0.26)	0.66 (0.22)

MMR = Mixed Multilevel Regressions; UC = Usual Care; SC = Specialised Care; mo = months

Cost-effectiveness

The results of the cost-effectiveness analyses are presented in table 4. In the base case analysis the mean incremental cost-effectiveness ratio amounts to €8,375 per QALY gained from a health care perspective, and €19,688 per QALY gained from a societal perspective (Table 4). Based on these results, SC can be considered cost-effective as opposed to UC.

The sensitivity analyses show slightly more beneficial results. When using the predicted values from the mixed regression to handle missing values in the HUI scores, the incremental cost-effectiveness ratios are slightly lower. In the complete cases analysis the incremental cost-effectiveness ratio is lower from a health care perspective, but higher when adopting the societal perspective.

In the analyses conducted from a societal perspective, the uncertainty surrounding the incremental costs and effects is considerable (See Appendix A for cost-effectiveness planes en cost-effectiveness acceptability curves). In the base case analysis, from the health care perspective the probability that SC is cost-effective is 68% for a willingness to pay for a QALY of €35,000. From the societal perspective, the probability that SC is cost-effective is 57% for a willingness to pay for a QALY of €35,000. The sensitivity analyses show slightly more favorable results for SC, except for the complete cases analysis from a societal perspective for which the probability that SC is cost-effective is 52% for a willingness to pay for a €35,000.

TABLE III. MEAN COSTS PER PATIENT IN USUAL CARE (N=247) AND SPECIALISED CARE (N=245)

Cost component	Unit costs €	Mean costs*			
		N	SC	N	UC
Health care costs			3231		3110
increment			*122*		
First level tinnitus care			1675		1480
Pure tone audiometry	32.42[a]	240	66.30	242	65.23
Speech audiometry	22.66[a]	240	46.34	242	45.60
Tympanometry: incl. stapedial reflexes	26.94[a]	240	55.09	242	54.21
Tinnitus analysis: PMF, MML	14.87[a]	240	30.41	242	29.92
Uncomfortable Loudness Levels	59.84[a]	240	122.37	242	120.41
Individual consult by clinical physicist in audiology	145.02[a]	240	296.55	242	291.80
Hearing aid fitting	351.00[c]	63	154.90	63	150.20
New hearing aid	831.00[b]	46	271.35	45	252.33
Hearing aid check and optimisation	98.00[a]	90	60.40	125	86.10
Fitting tinnitus masker	350.00[d]	45	102.86	55	111.94
New tinnitus masker	1000.00[d]	37	253.06	46	259.11
BERA	152.71[a]	19	11.84	19	11.75
Intake psychologist	222.50[a]	211	191.62	1	0.65
Tinnitus Educational Group session	13.15[e]	211	11.49	2	0.90
Second level tinnitus care			555		292
Individual trajectory	348.25[e]	10	14.21	-	-
Treatment group A	1186.45[e]	41	198.55	-	-
Treatment group B	2023.37[e]	34	282.18	-	-
Social work trajectory (incl. intake)	318.19[a]	22	61.09	96	292.43
General practitioner practice			78		133
GP visit	28.00[f]	95	40.21	129	67.74
GP home visit	43.00[f]	45	17.31	65	31.07
GP assistant visit	14.00[f]	62	10.64	76	17.35
GP weekend and evening	59.56[g]	22	10.22	32	16.91
Hospital care			384		450
ENT specialist visit	129.00[f]	95	172.53	117	192.68
Neurologist visit	129.00[f]	37	41.67	45	54.11
Dental surgeon visit	129.00[f]	14	13.58	19	22.28
Other medical specialist	129.00[f]	55	156.41	79	181.26
Other health care professionals			540		753
Physiotherapist	36.00[f]	104	121.14	122	179.65
Psychologist	171.00[f]	74	119.68	94	182.33
Psychiatrist	129.00[f]	42	48.07	53	58.74
Social worker	65.00[f]	48	31.66	74	48.21
Occupational therapist	22.00[f]	19	3.91	30	8.21
Company doctor	129.00[f]	79	143.95	87	166.57
Homeopath	10.00 – 82.50[h]	54	19.71	67	33.75
Acupuncturist	20.00 – 93.33[h]	54	22.83	71	33.08

Haptonomist	12.50 – 40.00 [h]	36	4.23	48	11.87
Magnetizer / Faith healer	28.00 – 50.00 [h]	38	0.92	45	2.32
Prescribed medication					
Medication	Various[b]	79	23.55	84	29.18
Patient & family costs			85		108
Over the counter medication	Various[h]	78	4.95	84	8.18
Travelling expenses	Various[h]	138	3.61	153	4.57
Sports, meditation or other costs	5.00 - 1200.00[h]	112	76.71	119	95.80
Productivity losses			2605		2417
Loss of productivity at paid labour	Mean /hour[f]	128	2604.82	128	2417.43
Total societal costs			5921		5636
Increment			286		

* Missing value analysis based on multiple imputation
[a] Anonymous source; [b] GIP databank 2009; [c] www.nvab.nl; [d] oral communication with several hearing aid dispensers; [e] cost calculation; [f] Hakkaart et al. 2010; [g] www.nza.nl/regelgeving/tarieven; average tariff 2009 calculated for Limburg; [h] cost questionnaire. PMF = Pitch Match Frequency; MML = Minimum Masking Level

TABLE 4. COST-EFFECTIVENESS ANALYSIS

Analysis		Incremental result mean/patient	Uncertainty				
			Bootstrap 95% confidence interval	Distribution on the cost-effectiveness plane			
				NE	**SE**	**SW**	**NW**
Multiple Imputation	Health care Costs	€ 122	€ -267 to € 515				
	QALY	0.0145	-0.028 to 0.055				
	iCER	€ 8,375		52%	22%	4%	22%
	Societal Costs	€ 286	€ -828 to € 1,427				
	QALY	0.0145	-0.028 to 0.055				
	iCER	€ 19,688		48%	20%	6%	27%
QALY Based on MRR	Health care Costs	€ 122	€ -267 to € 515				
	QALY	0.017	-0.019 to 0.057				
	iCER	€ 7,369		60%	13%	6%	21%
	Societal Costs	€ 286	€ -828 to € 1,427				
	QALY	0.017					
	iCER	€ 17,323		55%	13%	6%	21%
Complete Cases analysis	Health care Costs	€ 231	€ -256 to € 707				
	QALY	0.029	-0.028 to 0.080				
	iCER	€ 8,065		68%	15%	1%	16%
	Societal Costs	€ 802	€ -754 to € 2,389				
	QALY	0.029	-0.028 to 0.080				
	iCER	€ 28,041		67%	15%	1%	17%

QALY = Quality Adjusted Life Year; iCER = incremental Cost Effectiveness Ratio

Discussion

This article reports on what is, to our knowledge, the first full economic evaluation of a multidisciplinary stepped care approach to tinnitus treatment combining TRT and CBT. In both groups utility values decrease in the first three months. This could be a result of increasing awareness of the tinnitus in the first months of treatment. After the first three months, in SC utility values increase up to 12 months, while, in contrast, the UC utility values further decrease. This implies that the SC has a long-term positive effect on health related quality of life, while the UC seems to have a negative effect. Other studies found that treatments based on TRT or CBT, which were an important part of the SC, were effective up to 15 years after the therapy ended (Forti, et al., 2009; Goebel, Kahl, Arnold, & Fichter, 2006; Lux-Wellenhof & Hellweg, 2002; Zachriat & Kroner-Herwig, 2004). It would be interesting to know the longer term effects of SC on health related quality of life. The long term negative effect in the UC seems to be a result of the fact that quality of life in tinnitus patients decreases if there is only little or no attention to psychological factors.

Costs associated with the tinnitus care in the audiological centre were considerably higher in SC. This was partly compensated by lower costs in SC for other tinnitus related health care costs. Productivity costs were higher in SC. This could be due to the fact that the SC is more time-consuming than the UC. Participants with paid jobs in one of the treatment groups of SC, were often absent from work during the treatment days. Moreover, in second level tinnitus care in SC it is advised to participants to, if on sick leave; resume their paid work only after the intervention is completed.

With regard to cost-effectiveness, the results show that SC costs society €19,688 per QALY gained based on the base case estimates of input parameters. Although there is no consensus about a reasonable threshold value for cost-effectiveness, the NICE guideline state that the reimbursement of interventions costing less than £30,000 (approximately €45,000) are generally never questioned (Devlin & Parkin, 2004; Raftery, 2001). The Dutch Council for Public Health and Health Care has set the threshold at €80,000 for diseases with a high burden (RVZ, 2006). The low quality of life scores at baseline (0.63) indicate that tinnitus is a relatively high burden to the patients that suffer from it. Therefore we consider the treatment to be cost-effective, despite the uncertainty surrounding the incremental costs and effects being substantial, in particular for the analyses from a societal perspective. If willingness to pay for an additional QALY amounts to €50,000, the probabilities that SC is the most cost-effective treatment are 60% (societal perspective) and 70% (health care perspective). Sensitivity analyses showed that the approach to handling missing values impacted on the results. However, it did not alter the conclusions.

Some limitations of this study need to be considered. First, the proportion of missing data and non-response was acceptable, however larger than expected. In the base case analysis it was assumed that data were missing at random but, at this level of missing data, we cannot rule out the possibility of non-random causes for dropout. Fortunately, the sensitivity analyses show that, although the approach to handling missing values does impact the results, the conclusions remain the same. Secondly, a longer time horizon may be necessary to identify relevant longer-term outcomes; especially since quality of life slightly improves at the last follow-up in the SC, and deteriorates in the UC. It is expected that a longer time horizon would show even more favourable results for the SC. In conclusion, this economic evaluation, conducted from a societal perspective using a one year follow-up period, shows that a specialized multidisciplinary tinnitus treatment based on cognitive behavioral therapy is more cost-effective than usual care.

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Competing Interest Statement

The authors have no competing interests to report

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Base Case Analysis

FIGURE A.1 COST-EFFECTIVENESS PLANE OF BASE CASE ANALYSIS FROM SOCIETAL PERSPECTIVE

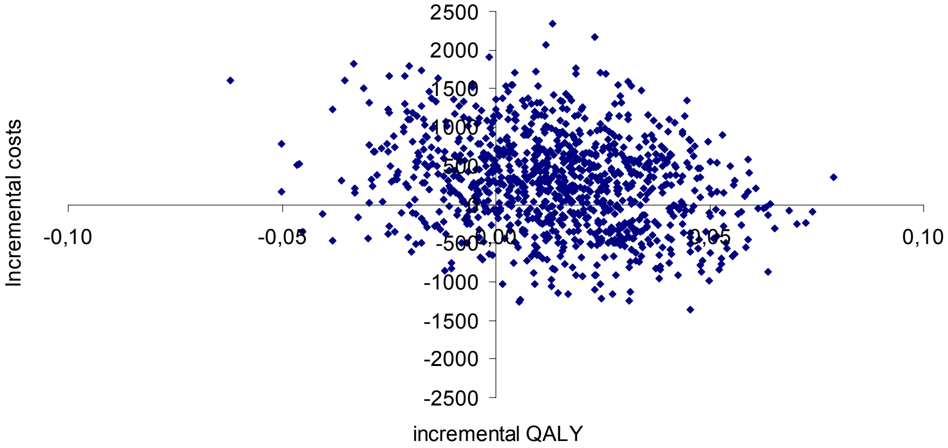


FIGURE A.2 COST-EFFECTIVENESS PLANE OF BASE CASE ANALYSIS FROM HEALTH-CARE PERSPECTIVE

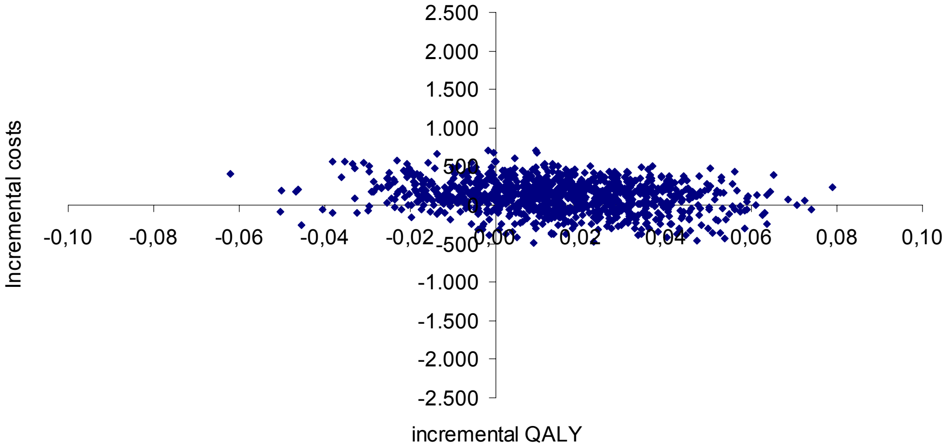
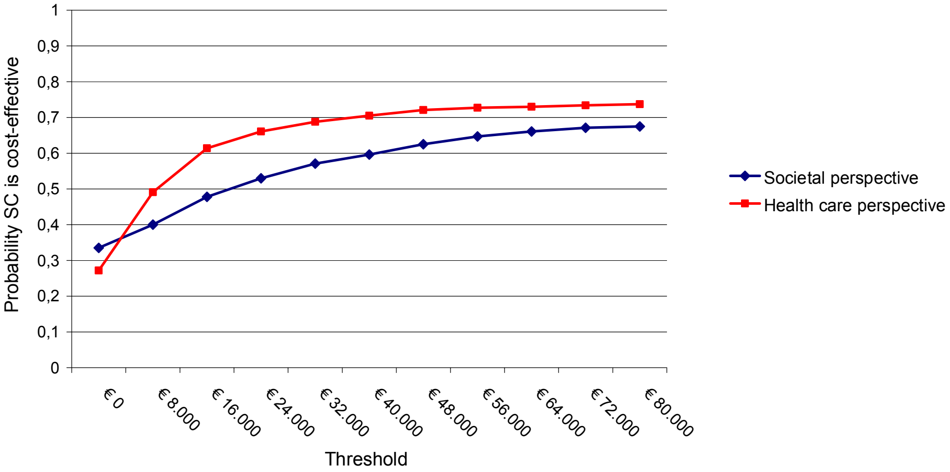


FIGURE A.3 COST-EFFECTIVENESS ACCEPTABILITY CURVES BASED ON BASE CASE ANALYSIS



Sensitivity analysis I

FIGURE A.4 COST-EFFECTIVENESS PLANE FORM SOCIETAL PERSPECTIVE OF SENSITIVITY ANALYSIS IN WHICH MISSING VALUES ON HUI WERE BASED ON PREDICTED VALUES FROM MULTIPLE MIXED REGRESSION

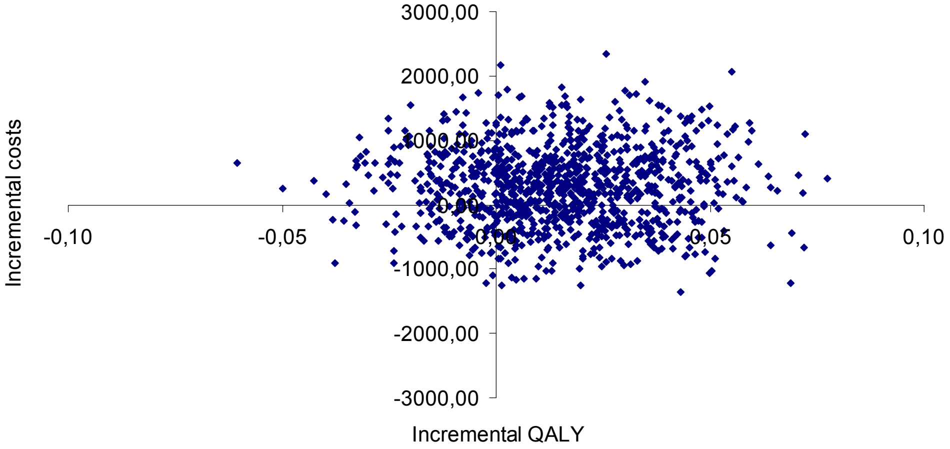


FIGURE A.5 COST-EFFECTIVENESS PLANE FORM HEALTH-CARE PERSPECTIVE OF SENSITIVITY ANALYSIS IN WHICH MISSING VALUES ON HUI WERE BASED ON PREDICTED VALUES FROM MULTIPLE MIXED REGRESSIONS

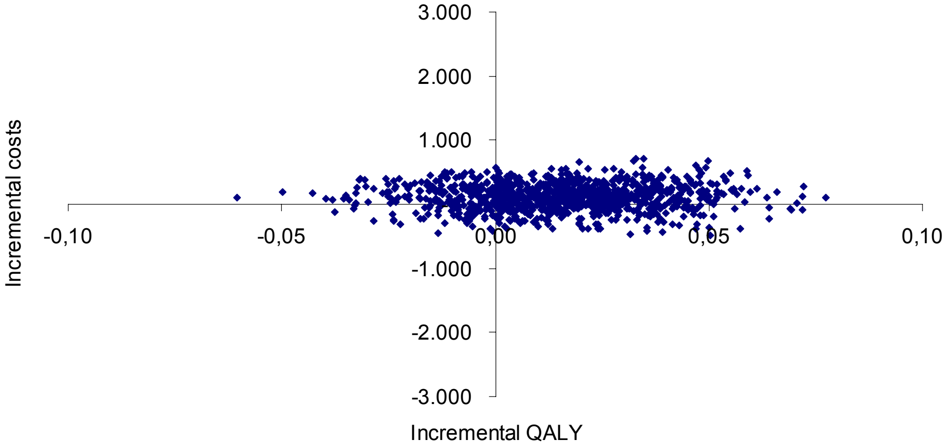
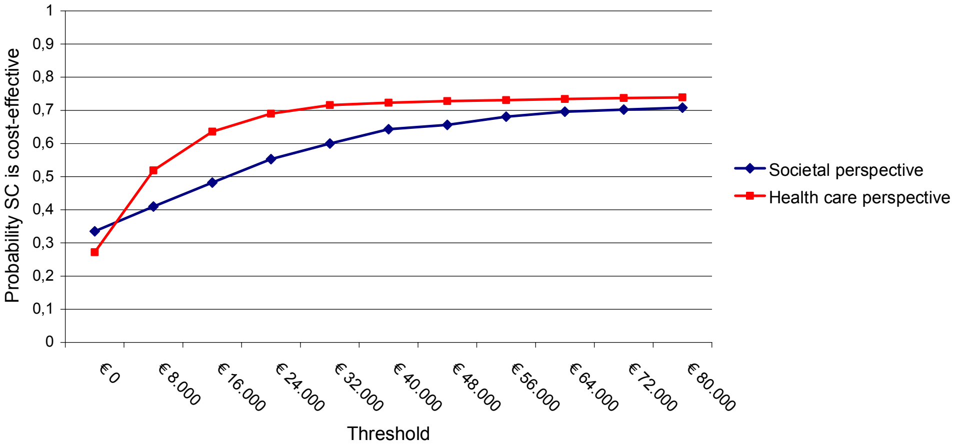


FIGURE A.6 COST-EFFECTIVENESS ACCEPTABILITY CURVES BASED ON SENSITIVITY ANALYSIS IN WHICH MISSING VALUES ON HUI WERE BASED ON PREDICTED VALUES FROM MULTIPLE MIXED REGRESSION



Sensitivity analysis II

FIGURE A.7 COST-EFFECTIVENESS PLANE FORM SOCIETAL PERSPECTIVE OF COMPLETE CASES ANALYSIS

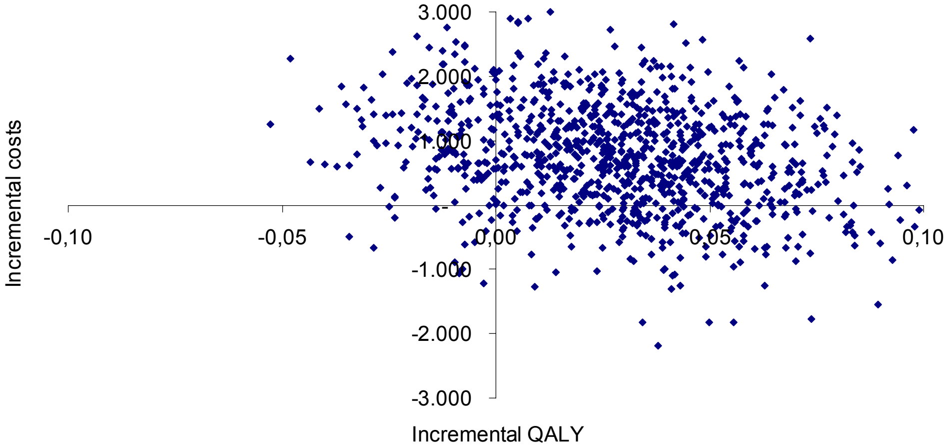


FIGURE A.8 COST-EFFECTIVENESS PLANE FORM SOCIETAL PERSPECTIVE OF COMPLETE CASES ANALYSIS

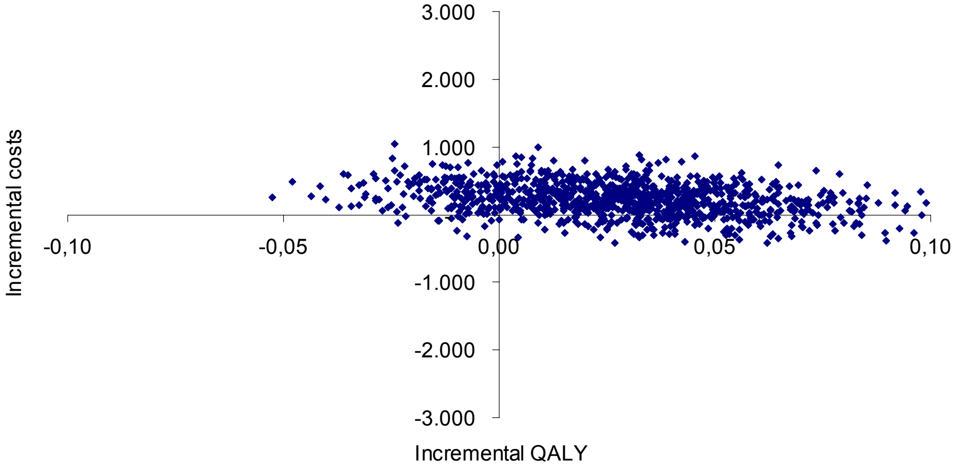
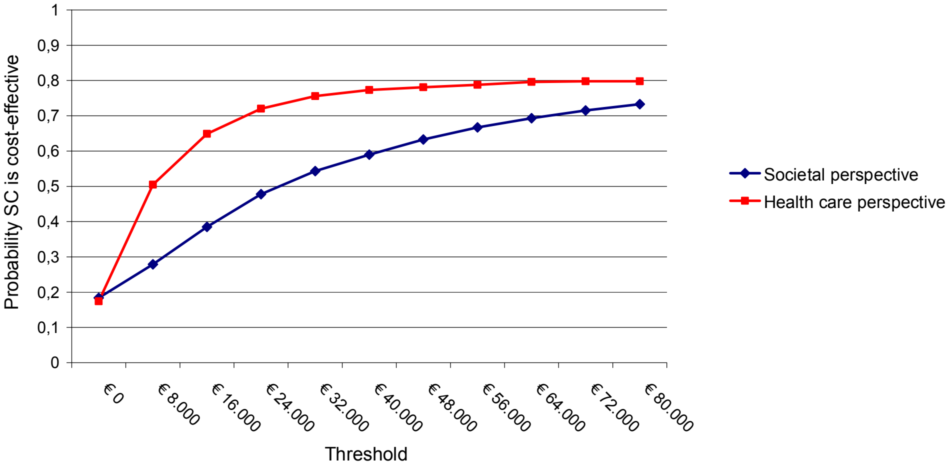
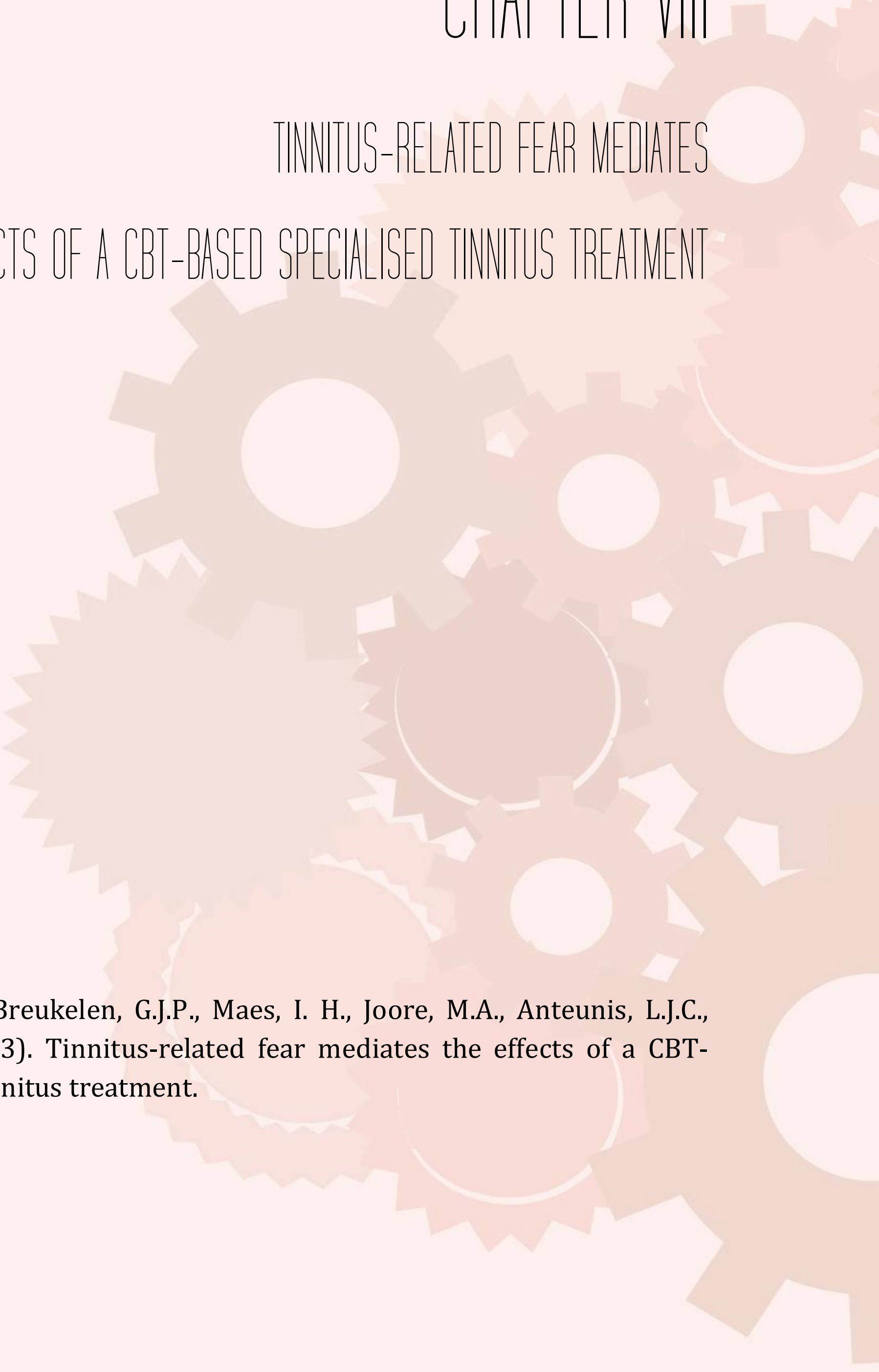


FIGURE A.9 COST-EFFECTIVENESS ACCEPTABILITY CURVES BASED ON COMPLETE CASES ANALYSIS



CHAPTER VIII

TINNITUS-RELATED FEAR MEDIATES THE EFFECTS OF A CBT-BASED SPECIALISED TINNITUS TREATMENT



Submitted as

Cima, R. F. F., van Breukelen, G.J.P., Maes, I. H., Joore, M.A., Anteunis, L.J.C., Vlaeyen, J.W.S. (2013). Tinnitus-related fear mediates the effects of a CBT-based specialised tinnitus treatment.

Abstract

Objective: Cognitive behavioural approaches (CBT) in the alleviation of tinnitus complaints have been shown to be effective; however the specific mechanisms of change are yet to be unveiled. Reductions in tinnitus-related fear have been indicated to be an important factor in alleviating tinnitus suffering. The role of tinnitus-related fear is proposed as an important mediator explaining CBT stepped-care treatment effects on tinnitus severity, tinnitus-related impairment and general quality of life of tinnitus patients.

Methods: A two-group, single-centre RCT was carried out with adult tinnitus patients (n=492), with 3 follow-up assessments up to 12 months after randomization. Patients were randomly assigned to Usual Care (UC) or Specialized Care stepped care (SC). A repeated-measures design, with group as a between subjects factor, and time as the within-subject factor, was used in an intention-to-treat analysis. Mixed regressions for assessing mediation effects were performed with general health, tinnitus distress, tinnitus related impairment as the dependent variables and tinnitus related fear as the mediator variable.

Results: Tinnitus-related fear mediates the treatment benefits of specialized care, as compared to usual care, with respect to increased quality of life ratings, and decreased tinnitus severity and tinnitus related impairments (p<.001).

Conclusions: The effectiveness of CBT treatment approaches can be explained by significant reductions in tinnitus-related fear. These results are relevant in that currently, though CBT approaches in tinnitus management have been proven to lead to decreased suffering of tinnitus patients, the psychological mechanisms causing these benefits are still to be discovered.

Funding: Trial funding was supported by The Netherlands Organisation for Health Research and Development (ZonMW). Research programme: Health Care Efficiency, Subprogram: Effects & Costs, Grant number: 945-07-715, Grant applications round 2007.

Key words: Tinnitus-related fear, mediation, cognitive behaviour therapy, RCT, Fear-avoidance

Introduction

Up to 21 percent of the adult population is at one point in life bothered by tinnitus, an internally generated noxious sound (Krog, Engdahl, & Tambs, 2010). The larger part of this group habituates to the tinnitus fairly easily, however for up to 6% of this group the tinnitus becomes a noxious and disabling problem considerably impacting all aspects of daily living. (Cima, Vlaeyen, Maes, Joore, & Anteunis, 2011; Erlandsson & Hallberg, 2000; Javaheri, Cohen, Libman, & Sandor, 2000; Moller, 2010) Psychological impairments such as cognitive dysfunctions, attentional deficits and severe emotional disturbances as a result of the tinnitus which are most troubling for patients, are considered the key factors in predicting the level of tinnitus suffering and the decrease in quality of life (Andersson & Westin, 2008; Erlandsson & Hallberg, 2000; Hallam, McKenna, & Shurlock, 2004). Interestingly, audiometric properties of the tinnitus (loudness or pitch) hardly predict annoyance of the tinnitus or impact of tinnitus on daily living (Andersson, 2003; Hiller & Goebel, 2006, 2007).

A widely accepted tinnitus treatment approach tinnitus retraining therapy (TRT) is based on a neurophysiological (NP) model (Jastreboff & Jastreboff, 2006). One of the main assumptions of the NP model is that conditioned fearful reflexes in processing the tinnitus sound predict dysfunctional habituation processes in disabling tinnitus (Jastreboff, 1990; Jastreboff & Hazell, 1993; Jastreboff & Hazell, 2004). TRT is aimed at enhancing habituation towards the noxious tinnitus sound, by exposing tinnitus patients to an external neutral sound, which is then hypothesized to generalize to the threatening tinnitus. Evidence for the TRT approach is equivocal however, and most of the published reports derive from retrospective and uncontrolled trials (Hiller & Haerkötter, 2005; Hoare, Stacey, & Hall, 2010; Phillips & McFerran, 2010). Alternatively, the hypothesis that the aversive psychological reactions to the sound might be more disabling than the sound itself has led to the second main tinnitus treatment approach; cognitive behavioural therapy (CBT), which is aimed at decreasing the psychological distress associated with chronic tinnitus (Andersson, 2002; Andersson, Juris, Classon, Fredrikson, & Furmark, 2006; Andersson & Verblad, 2000; Cima, Crombez, & Vlaeyen, 2011; Westin, Ostergren, & Andersson, 2008). Expanding on basic learning principles of the NP model, with a focus on the association between the interpretation of the signal and heightened negative emotional reflexes, a cognitive-behavioral account additionally incorporates behavioral reactions as a result of fearful responses. Accumulating evidence supports that CBT-based treatment approaches reduce suffering and improve quality of life in tinnitus suffering considerably (23-26). The specific mechanisms that account for the effectiveness of CBT approaches in tinnitus patients are still largely unknown however (Andersson & Westin, 2008).

Within the realm of the CBT approach, fear-related safety behaviours have been postulated to be an important factor in explaining increased suffering in tinnitus patients. Evidence has been found that the tendency to avoid unsafe activities because of the tinnitus, mediates the association between tinnitus severity and quality of life (Westin, Hayes, & Andersson, 2008; Westin, Ostergren, et al., 2008; Westin, et al., 2011). This was corroborated in a later study , in which it was found that fear of bodily sensations was strongly related to tinnitus distress, again fully mediated by tinnitus related avoidance behaviours (Hesser & Andersson, 2009). These findings indicate tinnitus-related fear as an important mechanism, possibly explaining why in some but not all patients, severe tinnitus suffering is such a persistent condition. Indeed, it has been indicated earlier that tinnitus-related fear has a mediating role in explaining increased quality of life (Cima, Crombez, et al., 2011). Interestingly, fear and fear-related safety behaviours are seen as the main mechanism in chronic pain suffering, and parallels between chronic pain and chronic tinnitus have been theorized before (Cima, Crombez, et al., 2011; Folmer, Griest, & Martin, 2001; Jastreboff, 1990; Tonndorf, 1987). Both conditions cannot be understood on biomedical grounds only, complete recovery is very rare, and complaints persist over long periods of time. The fear avoidance model (FA) of chronic pain predicts that, if pain is (mis)interpreted as threatening, it will elicit specific pain-related fear associated with protective escape and avoidance behaviour (Crombez, Eccleston, Van Damme, Vlaeyen, & Karoly, 2012; Leeuw, et al., 2007; Vlaeyen & Linton, 2000, 2012). These safety-seeking behaviours may be helpful in the short-term, but worsen the problem in the long run by increasing disability and negative mood (Gheldof, et al., 2010). There is ample empirical support for the role of pain-related fear in the development and maintenance of the suffering of patients with chronic pain, both experimentally as well as clinically (Asmundson, Norton, & Allerdings, 1997; Crombez, Vlaeyen, Heuts, & Lysens, 1999; Dawson, Schluter, Hodges, Stewart, & Turner, 2011; de Jong, Vlaeyen, Onghena, Goossens, et al., 2005; den Hollander, et al., 2010; Gheldof, et al., 2010). Moreover, recent evidence seems to indicate that pain-related fear acts as a mediator between pain severity, intensity, negative mood and pain disability (Gheldof, et al., 2006; Kamper, et al., 2012; Meulders, Vansteenwegen, & Vlaeyen, 2012).

In the current study we predicted that aversive reactions towards the tinnitus sound, and tinnitus-related fear in particular might be the key factor in predicting tinnitus disability and its impact on daily living. We expect that tinnitus related fear might not only be the mediating factor in the maintenance of chronic tinnitus distress, but could also explain the positive effects of a specialised CBT-based treatment on tinnitus severity, tinnitus related impairment and quality of life, as was shown in a recent RCT (Cima, et al., 2012).

The effectiveness of a specialised stepped-care tinnitus-treatment approach based on cognitive behavioural therapy (CBT) was demonstrated by improved quality of life, decreased tinnitus severity and daily life impairment by tinnitus as compared to the treatment as usual. Moreover, the CBT-based tinnitus treatment generated greater improvements in general negative emotions, level of tinnitus-related cognitive difficulties, and tinnitus-related fear (Cima, et al., 2012). The stepped-care CBT-based treatment for tinnitus included cognitive restructuring methods, exposure techniques, applied relaxation, ACT, mindfulness elements and stress-relief techniques. These methods were combined with audiological TRT counselling, directed more towards the sound perception level of tinnitus, and organised in 2 steps, increasing the level of treatment intensity as complaints were more severe (Cima, et al., 2012; Von Korff & Moore, 2001).

Methods

In the present study data were used obtained from an earlier randomized controlled study, in which the effectiveness of CBT based specialised tinnitus treatment (SC) compared to usual care (UC) was investigated (Cima, et al., 2009). Brief descriptions of the study design, participants, intervention procedures, outcomes, and statistical procedures, relevant for the present study, are provided below.

Study design

A two group, 2- stepped care, single-centre randomized controlled trial was carried out with adult tinnitus patients, with 3 follow-up assessments up to 12 months after randomization, with a no-contact period in the last 4 months in the trial, between follow up 2 and follow up 3. Tinnitus patients referred to our specialised tinnitus centre were, after screening, invited to participate during a time period of 16 months. Patients willing to participate were invited for a first off-centre assessment contact, after which they were randomly allocated to either to Usual Care (UC) or Specialized Care (SC). The Medical Ethical Board of the Rehabilitation Foundation Limburg reviewed and approved of the study protocol (METC-SRL: 11/09/2006) and the trial was funded by ZonMw, Grant number: 945-07-715. The trial has been registered at ClinicalTrial.gov, (registration number NCT00733044).

Participants

All patients referred to our centre who reported subjective tinnitus complaints, aged 18 years and older, were eligible for inclusion. Patients were excluded when unable to read and write in Dutch or when medical conditions prevented them to participate. Also excluded were patients who visited our centre within 5 years prior to trial enrolment. An ENT physician assessed all patients before entering the trial, and examined the presence of acute audiological conditions, requiring immediate medical care. Written informed consent was obtained before assessment and trial entry and both patients and assessors were blinded for treatment allocation.

Intervention procedures

CARE AS USUAL (UC)

The Usual Care procedure entailed a standardized protocol modelled after the average care as is usually provided by secondary care audiological centres across the Netherlands. Step-1 of UC treatment consisted of a standard audiological intervention (sound-generators were prescribed when specifically asked for by the patient). For patients with mild complaints, treatment ended after step 1, and they remained in the trial without additional treatment. In case tinnitus suffering was more severe (as measured at baseline and after audiological counselling), patients could enter a second step of treatment for 12 weeks maximally (Cima, et al., 2012).

SPECIALISED CARE (SC)

Specialised Care consisted of comprehensive multidisciplinary diagnostics and treatment, offering specific principles from TRT (especially the counselling elements with use of the neuro-physiological model) within in a CBT framework (sound-generators were prescribed when specifically asked for by the patient). Step 1 treatment consisted of a TRT-based multidisciplinary intervention, carried out in a cognitive behavioural framework (including audiological rehabilitation when necessary). For patients with mild complaints this basic intervention was expected to suffice, and they were measured for follow-ups only and remained in trial without extra care. When tinnitus suffering was more severe (as measured at baseline and after psychological screening), patients could enter step 2 treatment, which consisted of three different 12-week group-treatment options (Cima, et al., 2012).

Outcomes

STRATIFICATION ASSESSMENT

To assess *hearing impairment* pure tone audiometry was performed bilaterally on 1, 2, and 4 kHz, using a mobile audiometer (Interacoustics AS208) with audiometry headphones (Telephonics TDH-39, Peltorcapped) and the pure tone average (PTA) for 1, 2 and 4 kHz (stratification cut-off point at 60 dB hearing level in worst ear) was calculated.

The Tinnitus Questionnaire was used to assess *Tinnitus-severity* at baseline (stratification cut-off point at a score of 47) (Rief, Weise, Kley, & Martin, 2005).

OUTCOME MEASURES

The HUI mark III is a 17 item questionnaire to assess *Health related quality of life* or Generic Health on eight dimensions: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain/complaints. Each question has five or six levels, and 972.000 possible health states can be computed. Possible utility scores range from -0·36 to 1·00 (Feeny, et al., 2002) for the HUI mark III. The HUI has shown adequate responsiveness in the tinnitus population (Maes, Joore, Cima, Vlaeyen, & Anteunis, 2011).

Tinnitus severity or distress due to the tinnitus was assessed with the Tinnitus Questionnaire (TQ) (Hallam, Jakes, & Hinchcliffe, 1988). The TQ consists of 52 items rated on a 3-point scale and assesses the psychological distress associated with the tinnitus. Psychometric properties of the TQ have proven excellent in different languages (Baguley, Humphriss, & Hodgson, 2000; McCombe, et al., 2001).

The tinnitus handicap inventory (THI) is a 25-item instrument scored on a 3 point Likert scale. The THI assesses *Tinnitus related impairment*, or negative responsiveness as a result of the tinnitus on 3 domains; functional, emotional and catastrophic (Newman, Jacobson, & Spitzer, 1996). Both overall and subscale internal consistency were found to be good (Newman, Sandridge, & Jacobson, 1998).

The Fear of Tinnitus Questionnaire (FTQ) measures *Tinnitus-related fear*. Of this novel measure, items were included that were believed to capture worries and fears of patients experiencing tinnitus (see appendix 2). Some of the FTQ items were derived from the Tampa scale for Kinesiophobia (Roelofs, et al., 2007) and the Pain Anxiety Symptoms Scale (McCracken, Zayfert, & Gross, 1992). The FTQ was pretested with patients. The FTQ has 17 items to be rated on a true or false scale. Internal consistency of the total FTQ score in the current sample was excellent as well (Cronbach's alpha = ·82). Demographic data were gathered by means of a 5-item questionnaire to establish gender, age, duration of complaints, educational level and adherence area.

Statistical analysis

All statistical analysis were performed with PASW SPSS statistical software, version 18·0 (SPSS, 2009).

TREATMENT OUTCOME: INTENTION-TO-TREAT ANALYSES

Intention-to-treat analyses were employed. That is, all patients who were measured at baseline and allocated to treatment initially were included, irrespective of their participation in subsequent treatment or follow up measurements. A series of mixed (multilevel) regression analyses was carried out on all available data, without imputation of missing data. The outcome measures were used as dependent variables in a repeated measures mixed analysis with group (US, SC) as the between-subject factor and time (Baseline, follow up 1, follow up 2 and follow up 3) as the within-subject factor. Age, gender, education, and the stratifiers were included as covariates to increase statistical power. Since duration of complaints was a potentially relevant prognostic variable, this was added to the model as well[6]. See appendix A for details on the mixed model.

MEDIATING MECHANISMS

Figure 1 graphically represents the mediator model. To test whether changes in tinnitus-related fear mediated the treatment effect (SC versus UC) on the outcomes, we extended the final mixed model (see appendix A) from the intention to treat analysis with the mediator using McKinnon's joint significance test (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002), consisting of two separate analyses. First, the effect of the treatment on tinnitus-related fear was tested. This was done using mixed regression in the outcome analyses with the FTQ as an outcome variable. (Cima, et al., 2012). Second, we tested the effect of tinnitus-related fear on the primary outcomes; general health, tinnitus severity, and tinnitus related impairment, controlling for treatment. This was done by adding the mediator to the final mixed models for the HUI, the TQ, and the THI as a time dependent (within-subjects) covariate. So the baseline mediator value served as a covariate for the baseline outcome measurement, the first follow up value of the mediator as a covariate for the first follow up of the outcome and so forth. This analysis also checked the presence of mediator by time interaction by adding the product term of mediator and time as predictor.

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[6] Categorical covariates were entered in the model using dummy coding, for Gender: 0 = male, 1 = female; Education dummy 1: 0 = low, 1 = middle, 0 = high; education dummy 2: 0 = low, 0 = middle, 1 = high. Each quantitative covariate was first entered centred (Cov – sample mean = CovCen), and subsequently we added its square (CovCen * CovCen = CovCen2) to the model to assess possible nonlinear effects of the covariates on the outcomes.

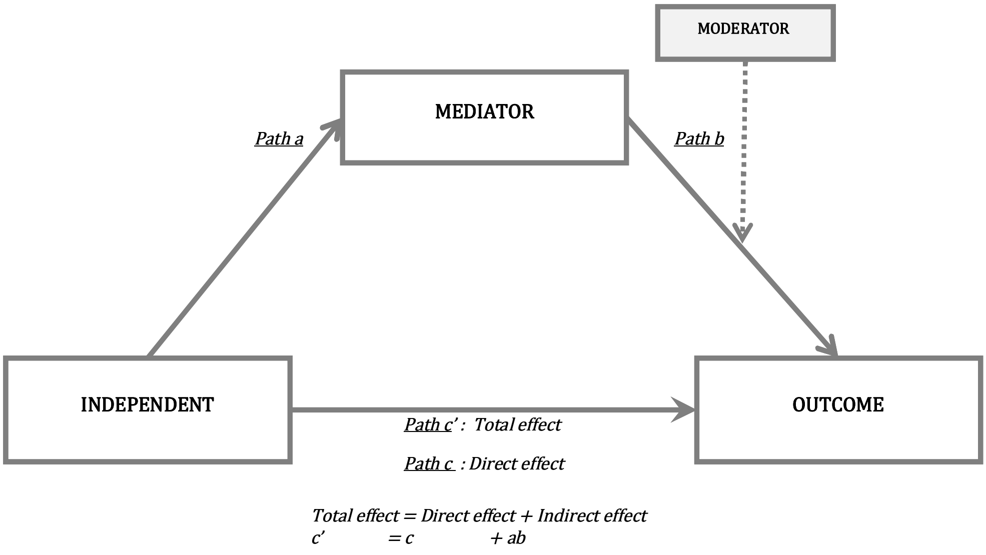


FIGURE 1. THE MEDIATOR MODEL

Joint significance holds if the associations between treatment and mediator in the first analysis (path *a*), and between mediator and outcome in the second analysis (path *b*), are both significant. Of course, interpreting such significance as evidence for mediation can only occur under the assumption that there are no hidden confounders affecting mediator and outcome simultaneously. (Emsley, Dunn, & White, 2010).

A delay in effect of the mediator on the outcomes was investigated as well, by using the mediator value at time point t as predictor of the outcome at time t+1. In these analyses only part of the data could be used since there is no mediator available for the outcome at baseline and there is no outcome available for the mediator at the last time point. So the baseline mediator value served as a covariate for the first outcome measurement, the first follow up value of the mediator as a covariate for the second follow up of the outcome, and so forth.

Last, a moderating effect of step 2 treatment (i.e. whether or not patients actually had received treatment in the 2nd step or not after follow up 1) on the mediating role of fear was investigated, by repeating the mediation analyses on the outcomes HUI and THI, and adding as predictors the moderator itself and the interaction term (moderator x mediator) to the final model of the mediation analysis. We did not test the moderated mediation of treatment effects as measured with the TQ, since the baseline score on the TQ was the main indicator for receiving step 2 treatment (the moderator), which would lead to collinearity of the outcome and the moderator.

Results

Results obtained in the earlier RCT, the flow of participants and the treatment outcome analyses, which are relevant for current analyses, are described briefly below first (Cima, et al., 2012).

Flow of participants and treatment outcome analyses

Of the 741 participants who were screened for eligibility, 626 were invited for participation, and 492 completed baseline measurements and were then randomized to treatment step-1; of whom 247 were allocated to UC, and 245 to SC treatment. Randomization and allocation started in September 2007 and ended in December 2009. Follow-up measurements were completed in January 2011.

Non-response and drop-out rates per time point did not differ between groups ($\alpha = \cdot 01$, $p > \cdot 20$ on any of the time points, and did not appear to be related to demographics or outcomes, according to logistic regression per time point, using non-response and drop-out per time-point (0 = not missing, 1 = missing) as the outcome variable, and treatment group, all covariates (age, gender, education, duration of complaints, tinnitus-severity at baseline and hearing loss) and scores on the HUI, the TQ and the THI on the previous time-point as independent variables. Table 1 presents a summary of demographic characteristics of the study sample.

Table 2 displays the observed means and standard deviations of the HUI, the TQ, the THI, and the FTQ for all 4 time points (baseline, follow up 1, 2, and 3). Table 3 shows the estimated group differences, as well as the confidence intervals and effect sizes for all 3 follow up measurements. Significant group differences were found on all outcome measures. Group differences favouring SC in health related quality of life (HUI) were significant at both the second and third follow up assessment ($p < \cdot 05$ and $p < \cdot 01$ at 8 and 12 months after baseline respectively). Significant SC treatment effects in tinnitus severity (TQ) and in tinnitus related impairment (THI) were found on all 3 follow up assessments (p < ·01 at 3 months after baseline, and p < ·001 at 8 and 12 months after baseline). Significant SC treatment effects were found as well on all three follow up measurements of tinnitus related fear (FTQ) (p < ·01 at 3 months after baseline, p < ·001 at 8 and 12 months after baseline).

TABLE 1. SUMMARY OF DEMOGRAPHIC CHARACTERISTICS, BASELINE MEAN VALUES ON PRIMARY AND SECONDARY OUTCOME MEASURES, TINNITUS CHARACTERISTICS, AND AUDIOMETRIC DATA OF THE ALL PARTICIPANTS, AND FOR EACH GROUP SEPARATELY

	Total (n = 492)		**UC (n = 247)**		**SC (n = 245)**	
Age in yrs (SD)	54·19	(11·54)	54·63	(12·02)	53·74	(11·05)
Gender (% male)	62·6		60·7		64·6	
Education (%)						
Low	45·7		47·3		44·0	
Middle	27·7		24·5		30·9	
High	26·6		28·2		25·1	
Employment (% yes)	53·4		50·2		56·6	
Duration (%)						
less than 1 yr	29·9		32·7		27·2	
1 to 5 yrs	38·9		37·9		39·9	
more than 5 yrs	31·1		29·4		32·9	
Mild complaints TQ < 47 (%)	45·5		45·3		45·7	
Tinnitus sound: pure tone (%)	14·5		9·9		17·8	
Tinnitus left (ear/head) (%)	25·0		24·8		25,2	
Tinnitus right (ear/head) (%)	19·9		19·6		20·1	
Continuous tinnitus (%)	83·9		83·3		84·5	
Interval tinnitus (%)	6·9		3·0		10·7	
Fitting of hearing aid (% yes)	18·5		18·2		18·6	
Fitting of sound generator (% yes)*	18·9		18·6		19·2	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*
PTA right ear	29·74	19·40	30·30	20·58	29·18	18·15
PTA left ear	31·05	20·64	30·96	20·25	31·14	21·06
PTA bilateral	30·57	17·60	30·77	17·85	30·37	17·38

UC = Usual Care, SC = Specialized Care, PTA = Pure tone average (for 1, 2 and 4 kHz) *Sound generators were fitted by using a small band noise around the Pitch Match Frequency presented slightly below the tinnitus masking level (UC), or just above the hearing threshold, as measured with the small band noise of the sound generator (SC).

TABLE 2. OBSERVED MEANS AND STANDARD ERRORS (SE) BASED ON ALL AVAILABLE DATA FOR THE OUTCOMES AT BASELINE, FOLLOW UP 1 (AFTER STEP 1, 3 MONTHS AFTER BASELINE), FOLLOW UP 2 (AFTER STEP 2, 8 MONTHS AFTER BASELINE) AND FOLLOW UP 3 (4 MONTHS FOLLOW UP, 12 MONTHS AFTER BASELINE)

Outcome Measures	**Baseline UC (n=247)** **Baseline SC (n=245)**		**Follow up 1 UC (n=194)** **Follow up 1 SC (n=200)**		**Follow up 2 UC (n=161)** **Follow up 2 SC (n=175)**		**Follow up 3 UC (n=161)** **Follow up 3 SC (n=171)**	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Health related QoL (HUI)								
UC	0,641	0,019	0,640	0,021	0,634	0,023	0,631	0,022
SC	0,628	0,018	0,620	0,019	0,656	0,019	0,681	0,019
Tinnitus Severity (TQ)								
UC	48,87	1,22	45,51	1,41	42,36	1,55	42,12	1,56
SC	49,39	1,18	42,01	1,40	36,47	1,32	33,43	1,29
Tinnitus impairment (THI)								
UC	38,73	1,48	37,38	1,71	34,14	1,95	33,51	1,84
SC	39,25	1,45	34,25	1,66	28,85	1,55	26,45	1,45
Tinnitus related fear (FTQ)								
UC	7,32	0,23	6,60	0,27	6,19	0,32	6,04	0,32
SC	7,19	0,23	5,60	0,27	4,52	0,26	4,20	0,24

QoL = Quality of life, UC = Usual Care, SC = Specialized Care, SE = Standard Error, HUI = Health utilities index, TQ =Tinnitus questionnaire, THI = Tinnitus handicap inventory, FTQ = Fear of tinnitus Questionnaire

MEDIATION BY TINNITUS-RELATED FEAR

It has been already shown that there was a significant treatment effect on the presumed mediator, tinnitus related fear (path a), as SC treatment was more effective in reducing tinnitus related fear than UC treatment (see table 3). With respect to the relationship between fear of tinnitus as the mediator and the primary outcomes (HUI, TQ and THI), controlling for the SC-treatment effects on all 3 follow up assessments, we found a mediating effect of tinnitus related fear on health related quality of life (df = 1, p < ·001), tinnitus severity (df = 1, p < ·001), as well as on tinnitus related impairment (df = 1, p < ·001), where more than half of each of the total effects (paths c'), both at follow up 2 and 3, were mediated by tinnitus related fear (53, 61, and 61% respectively) and the remaining parts were direct effects (paths c).

TABLE 3. ESTIMATED GROUP DIFFERENCE (B) AND 95% CONFIDENCE INTERVALS (C.I.) ON OUTCOMES AT FOLLOW UP 1 (3 MONTHS), FOLLOW UP 2 (8 MONTHS), AND FOLLOW UP 3 (12 MONTHS), BASED ON INTENTION TO TREAT ANALYSIS

Primary outcomes	**B**	**95% C.I.**		**P**	**E.S. (absolute values)**
Health related QoL (HUI)[a]					
3 months	-0,009	0,056	0,039	0,6420	0,04
8 months	0,038	0,005	0,071	0,0258	0,18
12 months	0,059	0,025	0,094	0,0009	0,24
Tinnitus Severity (TQ)[b]					
3 months	-3,315	-5,612	-1,019	0,0048	0,20
8 months	-7,070	-9,561	-4,580	<0,0001	0,41
12 months	-8,062	-10,829	-5,295	<0,0001	0,43
Tinnitus impairment (THI)[c]					
3 months	-4,257	-7,065	-1,449	0,0031	0,32
8 months	-7,626	-10,713	-4,539	<0,0001	0,52
12 months	-7,506	-10,661	-4,352	<0,0001	0,45
Tinnitus related fear (FTQ)[d]					
3 months	-0,785	-1,486	-0,084	0,0039	0,35
8 months	-1,550	-2,353	-0,748	<0,0001	0,58
12 months	-1,502	-2,317	-0,688	<0,0001	0,48

QoL = Quality of life, UC = Usual Care, SC = Specialized Care, SD = Standard Deviation, HUI = Health utilities index, TQ =Tinnitus questionnaire, THI = Tinnitus handicap inventory, FTQ = Fear of tinnitus Questionnaire

1 Since UC is coded as 0 and SC as 1, a negative B shows lower scores in UC than SC at the follow up measurements. The B's displayed are the group * time effects as shown in appendix B, where time = 0 for baseline· time = 1 for follow up 1, time = 2 for follow up 2, and time = 3 for follow up 3

2 E.S. = Effect size, calculated by dividing the B's (ignoring their sign) by the square root of the average of residual variances at follow up 1, 2 and 3, giving a mixed regression version of Cohen's d.

a Adjusted for the main effects of both stratifiers(hearing loss and tinnitus severity at baseline), and of time (using dummy coding with baseline as reference category)

b Adjusted for the main effects of education, hearing loss, and time

c Adjusted for the main effects of age, duration, education, tinnitus severity at baseline and time, and for interaction effects of time by education and by tinnitus severity at baseline

d Adjusted for the main effects tinnitus severity at baseline, time, ,and for the interaction effects of time by tinnitus severity at baseline

Figure 2 graphically presents the mediator model with the regression weight for each path, in which *path a* is the effect of treatment on tinnitus-related fear, *paths b* are the effects of tinnitus related fear on quality of life, tinnitus severity, and tinnitus impairment respectively, controlling for treatment (SC versus UC), *paths c* are the direct effects of treatment the three outcomes respectively (i.e. controlling for the mediator tinnitus related fear), and the *paths c'* are the total effects of treatment on the outcomes. In table 4 the regression weights of paths a, b, and c for all three outcomes are listed for all three follow ups.

TABLE 4. REGRESSION WEIGHTS USED TO CALCULATE PATHS A, B, C AND C' OF THE MEDIATION MODELS FOR ALL THREE MAIN OUTCOMES

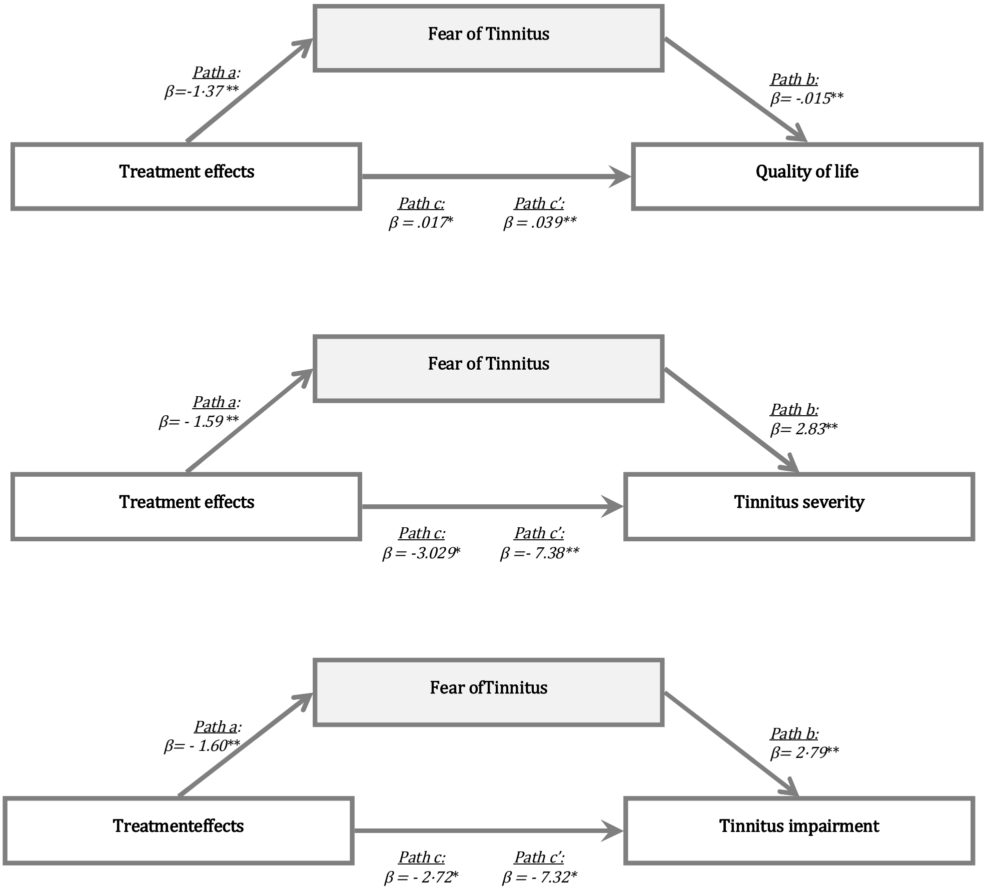
Paths	Term	HUI	TQ	THI
a	Group	-0.3366	-0.1553	-0.1571
	Group x Time	-1.0341	-0.7181	-0.7215
b	Mediator	-0.0165	2.9093	1.8764
	Mediator x Time	0.0014	-0.0375	0.4559
c	Group	-0.0204	0.7570	0.4080
	Group x Time	0.0371	-1.8933	-1.5632
c'	Group	-0.0110	2.9 x E-6	0.2359
	Group x Time	0.0499	-3.6938	-3.7762

Delayed mediation by tinnitus-related fear

After we found a cross-sectional mediating effect of tinnitus-related fear on the HUI and the TQ, the mediation analyses were repeated with FTQ values on the previous time point to investigate delayed mediating effects of tinnitus-related fear on quality of life, tinnitus-related impairment, and tinnitus severity. In this model the mediator measure at t was used as predictor for the outcome at t+1. Consequently, the baseline outcome recording was left out and so were all predictors concerning effects at baseline and one time indicator dummy. No delayed effect of fear of tinnitus was found on any of the three outcomes health related quality of life (HUI), tinnitus related impairment (THI), tinnitus severity (TQ) (all p > .40 for paths b).

Moderated mediation of tinnitus-related fear

We tested whether the mediation of treatment effects on HUI, and THI by tinnitus related fear was moderated by whether or not participants received step 2 treatment. Since the moderator itself (step 2 treatment yes/no) was mainly based on TQ baseline values, we did not test the moderated mediation on the treatment effects as measured on the TQ, for risk of high collinearity in the model. The moderated mediation effect might lead to too low statistical power for detecting mediation in the preceding analyses, for instance if mediation only occurs for patients receiving step 2 care such that the average mediation effect is diluted by the patients who did not receive step 2 care. We therefore repeated the mediation analysis, now including as moderator the indicator for step 2 care, and its interaction with the mediator , and its interaction with group as well, since moderation of path b implies moderation of at least one of the paths a, c, c' due to the constraint that c' = a*b + c (see figure 1), where the moderator was coded as (0,0,1,1) on the four successive time points for patients receiving step 2 care and as (0,0,0,0) else, irrespective of treatment condition, i.e. for both UC and SC. No moderated mediation was found, as the interaction term (moderator x mediator) was not significant for the HUI ($p >.06$). The moderated mediation of tinnitus related fear on treatment effects as measured with the THI remains indeterminate, since for we found a significant path b ($p < .001$), though paths a, c, and c' remained insignificant ($p > .70$). See figure 3 for the moderated mediation model and table 5 for the regression weights (see Appendix A for specifics).

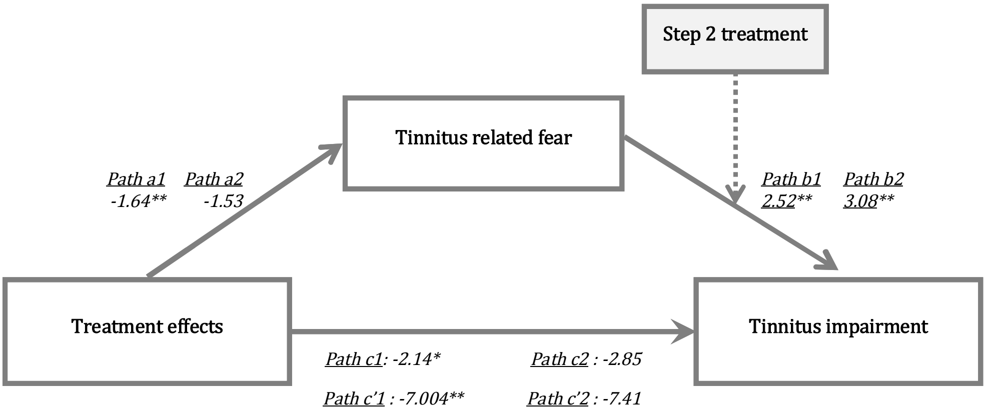


Note 1: *P < ·05 (2-tailed); **P < ·001 (2-tailed)
Note 2:The effects of path a, and the total effects (ç') differ from the intention to treat results in table 3, as a result of missing values and replacement of the 3 time dummies by a time variable coded (0, 0, 1, 1) for the HUI and (0, 1, 2, 2) for the THI. The betas are the effects on the last 2 follow ups. P
Note 3: the beta's for pathsa1, b1, c1 and c'1 are for the group that did not receive step 2, and paths a2, b2, c2 and c'2 for the group that did receive step 2. The Beta's for all paths can be inferred from the regression weights in table 5 given the time coding as provided.

FIGURE 2. THE MEDIATOR MODEL WITH TINNITUS RELATED FEAR (FTQ) AS THE MEDIATOR IN THE ASSOCIATION BETWEEN TREATMENT (SC VERSUS UC) AND QUALITY OF LIFE, TINNITUS SEVERITY, AND TINNITUS-RELATED IMPAIRMENT (THI) RESPECTIVELY. THE BETA'S OF INDIVIDUAL PATHS (A, B, AND, C) AND THE BETA OF THE TOTAL EFFECTS (C')

TABLE 5. REGRESSION WEIGHTS USED TO CALCULATE PATHS A, B, C AND C' OF THE MODERATED MEDIATION MODELS FOR THE TINNITUS HANDICAP INVENTORY (THI)

Path	Term	Beta's *without step2*	Path	Beta's *with step2*
	Group	-.1962		
	(Group x time)	(-7226)*2		
	Group x moderator			0.1138
a1		*-1.64042*	*a2*	*-1.5662*
	Mediator	1.623		
	(Mediator x time)	(0.4478)*2		
	Mediator x moderator			0.5729
b1		*2.5186*	*b2*	*3.0915*
	Group	0.8305		
	(Group x time)	-1.4899		
	Group x moderator			-.7035
c1		*-2.1493*	*c2*	*-2.8527*
	Group	0.5039		
	(Group x time)	(-3.7542) *2		
	Group x moderator			-0.4103
c'1		*-7.0042*	*c'2*	*-7.14*



Note 1: *P < ·05 (2-tailed); **P < ·001 (2-tailed). Note 2:The effects of path a, and the total effects (c') differ from the intention to treat results in table 3, as a result of missing values and replacement of the 3 time dummies by a time variable coded (0, 0, 1, 1) for the HUI and (0, 1, 2, 2) for the THI. The betas are the effects on the last 2 follow ups. Note 3: the beta's for pathsa1, b1, c1 and c'1 are for the group that did not receive step 2, and paths a2, b2, c2 and c'2 for the group that did receive step 2. The Beta's for all paths can be inferred from the regression weights in table 5 given the time coding as provided.

FIGURE 3. THE MODERATED MEDIATOR MODEL WITH TINNITUS RELATED FEAR (FTQ) AS THE MEDIATOR, AND STEP 2 PARTICIPATION AS THE MODERATOR ON THE B-PATH.

Discussion

The present study suggests that tinnitus-related fear plays a mediating role in the benefits of a CBT based approach in specialized tinnitus treatment (SC), when compared to usual audiological intervention (UC). Patients in the specialised treatment group increased their quality of life, decreased in tinnitus severity, and were significantly less impaired by their tinnitus, as compared to patients in the usual care group. The difference appeared to be partly due to decreased tinnitus-related fear in the SC group as compared with the UC group. We repeated the analyses to investigate whether mediation by tinnitus-related fear had a delayed effect, or depended on (was moderated by) receiving step 2 care. We did not find such a delayed effect of tinnitus related fear, but analyses revealed that the mediation effect of tinnitus related fear on treatment effects as measured with the THI is likely to be moderated by participation in step 2 treatment; however these last results remain inconclusive in the current analyses because of inconsistent results.

These findings also tentatively suggest that the beneficial reductions in tinnitus-specific impairment in the SC are mediated by reductions in tinnitus-related fear especially in those patients who actually participated in step 2, compared to those who did not. Earlier we found that tinnitus related fear explained about 61% of reductions in tinnitus related impairment, for the whole group, treated or untreated in step 2. We now find that for the patients who actually received step 2 treatment compared to those who did not, reductions is tinnitus related fear explained up to 68% of decreased tinnitus-impairment, however these results remain tentative, since we did not find significant moderator effects on the *a*, *c*, or *c'* paths. That we failed to show any moderated mediation effect on the HUI could be explained by the fact that this is a relatively general measure of quality of life. This measure might therefore be less sensitive to pick up the more specific tinnitus-related mechanisms of change (Maes, et al., 2011). In sum, decreased tinnitus-related fear in part explains why, the benefits of SC treatment significantly increased quality of life, and decreases tinnitus severity and impairment, when compared to the UC treatment group, irrespective of whether patients were treated in step 1 only, or were treated with an additional step. However, the role of decreased tinnitus-related fear becomes larger in explaining why tinnitus-related impairment in daily life decreases as a result of SC, when we compare those who received step 2 treatment to those who did not. These findings corroborate the notion that CBT has an attenuating effect on fear and fear related behaviours, thereby decreasing tinnitus complaints.

In the past, two main treatment approaches have dominated the management of patients with tinnitus complaints. The TRT approach, with a focus on sound habituation, as well as the CBT approach, with a focus on dysfunctional beliefs about tinnitus and associated safety behaviours, have been widely applied and studied (Henry, et al., 2007; Martinez Devesa, Waddell, Perera, & Theodoulou, 2007; Phillips & McFerran, 2010). A conceptual overlap between the widely accepted neurophysiological (NP) model and a cognitive-behavioural account of tinnitus suffering has been hypothesized earlier (Cima, Crombez, et al., 2011). The NP model postulates that in the generation and maintenance of chronic bothersome tinnitus, the perception and interpretation of the signal is strongly related to heightened negative emotional states, eliciting increased attention towards the tinnitus, enhancing the perception itself. The cognitive-behavioural perspective expands on these notions and incorporates the dysfunctional behavioural consequences of heightened tinnitus distress. Safety behaviours (avoiding loud environmental noise or silence, using hearing aids, or tinnitus masking devices, etc) may temporarily reduce the threat value of the tinnitus sound, but paradoxically reinforce fearful responding and increase tinnitus related disability in the long run. The cognitive-behavioural approach which has been successfully employed in treating chronic pain disorder (Vlaeyen & Morley, 2005), is considered to be quite similar for chronic tinnitus (Blaesing & Kroener-Herwig, 2012; Kleinstauber, et al., 2012). It has been shown that the novel CBT approaches in chronic pain, could offer new venues for research and management of chronic tinnitus as well (Cima, Crombez, et al., 2011). First, as in chronic pain (Vlaeyen & Linton, 2012), fear-related avoidance behaviours have been found to mediate the association between tinnitus severity and quality of life, moreover, avoidance behaviour was found to mediate the association between fear of bodily sensations and tinnitus related disability. Additionally, tinnitus-related fear has been found to mediate the association between cognitive misinterpretations of tinnitus and decreased quality of life. (Cima, Crombez, et al., 2011; Hesser & Andersson, 2009; Westin, Hayes, et al., 2008; Westin, et al., 2011)

Present findings support the importance of addressing tinnitus-related fear more systematically in the management of patients with disabling tinnitus. Our findings also support the conjecture that initial fearful responses towards the tinnitus sound, and as a result safety behaviours, may lead to more severe problems in the long run, not only decreasing chances for tinnitus habituation, but also maintaining the tinnitus impairment as such. Also, treatment effects might even be magnified when aiming treatment elements specifically at decreasing these fearful responses both in habituation based- as well as cognitive behavioural approaches, or as has been shown currently in a combination of both. Treatments aimed at fear reduction, such as exposure in vivo with behavioural experiments, have shown to be quite successful in the management of chronic pain (Bailey, Carleton, Vlaeyen, & Asmundson, 2010; de Jong, Vlaeyen, Onghena, Cuypers, et al., 2005; Vlaeyen, de Jong, Geilen, Heuts, & van Breukelen, 2002), and its application in tinnitus patients is warranted.

There are some considerations worth mentioning about the current study. *First*, the current CBT-based treatment consisted of a combination of CBT treatment elements, which of those contributed most to the overall effects, and specifically reductions in tinnitus related fear has remained unclear. A dismantling approach is recommended, leaving out potentially redundant treatment components in subsequent trials. *Second*, next to longitudinal studies, relying mostly on self-report measures, a more experimental approach, using behavioural and physiological measures, examining the nature of the threat value of the tinnitus sound, the fearful responses and behavioural reactions, will provide more fundamental insights into these processes.

In conclusion, our findings provide evidence that the effectiveness of CBT treatment approaches might be explained by significant reductions in tinnitus-related fear. Moreover, tinnitus related fear might explain why only a small part of individuals experience the heightened tinnitus distress and suffer prolonged chronic tinnitus, whereas for the larger part the tinnitus is hardly bothersome, since in them these fearful reactions might be absent. These results are highly relevant for clinical practice in that currently, though CBT approaches in tinnitus management have been proven to lead to decreased suffering of patients, the exact mechanisms causing these benefits are still to be discovered. Moreover, best practice for tinnitus in standard health care has of yet not been defined (Hoare, Gander, Collins, Smith, & Hall, 2010), which leads to fragmentized costly treatment trajectories (Cima, et al., 2009), often incorrect or insufficient information at the time of tinnitus onset, and mis-indication or delay of appropriate treatment, augmenting tinnitus related fear and fearful reactions aggravating tinnitus severity and suffering in a large group of patients.

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APPENDIX A: The mixed models for testing treatment effects and (moderated) mediator effects on the outcomes

Due to the randomization, pre-stratified on hearing loss and tinnitus severity, no significant baseline differences were expected between treatment conditions. However age, gender, education, hearing loss and tinnitus severity were included as covariates as to improve power. Since duration of complaints was a potentially relevant prognostic variable, this was added to the model as well[7]. The repeated measures per outcome were checked for multivariate outliers (mahalanobis distance, $p < \cdot 001$), and no such outliers were found for any outcome. Collinearity between covariates was checked but not found either, as all covariates had a variance inflation factor (VIF) below 1·5.

Since there were 4 repeated measures, time was entered in the mixed regression as a categorical variable using dummy coding[8], with the baseline as a reference category and a dummy indicator for every other time point (giving three dummies), to assess group differences in change from baseline, allowing for possible nonlinear change. To correct for multiple testing $\alpha = \cdot 05$ and $\alpha = \cdot 01$ (two-tailed) were used for primary and secondary outcomes, respectively.

The initial model included group, time, covariates, and group by time and covariate by time effects[9]. Each model change was tested for significance using Maximum Likelihood (ML) estimation and a likelihood ratio test with 'k' degrees of freedom (k = the difference in number of parameters between two successive models).

To enhance parsimony and increase interpretability of the model the following modelling steps were taken. First, every non-significant covariate by time interaction was removed, treating terms concerning the same predictor as one block with *d.f.* = 3 (e.g. *cov * followup1*, *cov* followup2*, and *cov * followup3* in the panel below). Second, covariates that were neither significant nor involved in a covariate * time term, were stepwise removed with *d.f.* = 1, again using the same restrictive α's. Third, the 'main' group effect (β_1 in the equation) was dropped from the model, which is a valid and power-improving step in randomized trials.(Laird & Wang, 1990; Van Breukelen, 2006)

Since baseline is the reference point, the 'main 'effect of 'group' actually reflects the group difference at baseline (see panel below). This effect is zero apart from sampling error due to randomization. The final mixed model per outcome was re-run with the restricted maximum likelihood method (REML) instead of ML to obtain better estimates of the standard errors. (Verbeke & Molenberghs, 2000)

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[7] Categorical covariates were entered in the model using dummy coding, for Gender: 0 = male, 1 = female; Education dummy 1: 0 = low, 1 = middle, 0 = high; education dummy 2: 0 = low, 0 = middle, 1 = high. Each quantitative covariate was centred (Cov – sample mean = CovCen) and its quadratic form (CovCen * CovCen = CovCen2) was added to the model to assess possible nonlinear effects of the covariates on the outcomes.

[8] For each time point except baseline (the reference category) a dummy indicator was entered in the model.

[9] Prior to the initial models we tested each covariate by treatment interaction over time with a separate mixed regression model per covariate, with three way interactions of group, covariate and time and all corresponding lower order terms. No such three way interactions were found.

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The mixed model equation for testing treatment effects on outcomes (See also Cima et al 2012)

$$y_{ti} = \beta_0 + \beta_1 \text{ group} + \beta_2 \text{ cov} + \beta_3 \text{ followup1} + \beta_4 \text{ followup}_2 + \beta_5 \text{ followup3} + \beta_6 \text{ group x followup1} + \beta_7 \text{ group x followup2} + \beta_8 \text{ group x followup3} + \beta_9 \text{ cov x followup1} + \beta_{10} \text{ cov x followup2} + \beta_{11} \text{cov x followup3} + e_{ti}$$

The mixed model equation for testing mediation effects on outcomes (same for delayed mediation, with as the mediator, the mediator values of the previous time point)

Equation for outcome without mediator total effect (c') and with the mediator as outcome (a)

$$y_{ti} = \beta_0 + \beta_1 \text{ group} + \beta_2 \text{ cov} + \beta_3 \text{ followup1} + \beta_4 \text{ followup2} + \beta_5 \text{ followup3} + \beta_{12} \text{ group x time} + \beta_{13} \text{ cov x time} + e_{ti}$$

Equation for outcome with mediator (paths b and c)

$$y_{ti} = \beta_0 + \beta_1 \text{ group} + \beta_2 \text{ cov} + \beta_3 \text{ followup1} + \beta_4 \text{ followup2} + \beta_5 \text{ followup3} + \beta_{12} \text{ group x time} + \beta_{13} \text{cov x time} + \beta_{14} \text{ med} + \beta_{15} \text{ med x time} + e_{ti}$$

The mixed model equation for delayed mediation

Equation for outcome without mediator total effect (c') and with the delayed mediator as outcome (a)

$$y_{ti} = \beta_0 + \beta_1 \text{ group} + \beta_2 \text{ cov} + \beta_4 \text{ followup2} + \beta_5 \text{ followup3} + \beta_{12} \text{ group x time} + \beta_{13} \text{ cov x time} + e_{ti}$$

Equation for outcome with the delayed mediator (paths b and c), without t=0, since t=1 is reference point

$$y_{ti} = \beta_0 + \beta_1 \text{ group} + \beta_2 \text{ cov} + \beta_4 \text{ followup2} + \beta_5 \text{ followup3} + \beta_{12} \text{ group x time} + \beta_{13} \text{ cov x time} + \beta_{16} \text{ Dmed} + \beta_{17} \text{ Dmed x time} + e_{ti}$$

The mixed model equation for testing moderated-mediation effects on outcomes

Equation for outcome without moderated mediator total effect (c') and with the mediator as outcome (a)

$$y_{ti} = \beta_0 + \beta_1 \text{ group} + \beta_2 \text{ cov} + \beta_3 \text{ followup1} + \beta_4 \text{ followup2} + \beta_5 \text{ followup3} + \beta_{12} \text{ group x time} + \beta_{13} \text{ cov x time} + e_{ti}$$

Equation for outcome with moderated mediator (paths b and c)

$$y_{ti} = \beta_0 + \beta_1 \text{ group} + \beta_2 \text{ cov} + \beta_3 \text{ followup1} + \beta_4 \text{ followup2} + \beta_5 \text{ followup3} + \beta_{12} \text{ group x time} + \beta_{13} \text{cov x time} + \beta_{14} \text{med} + \beta_{15} \text{ med x time} + \beta_{18} \text{mod} + \beta_{19} \text{ mod x med} + \beta_{20} \text{ mod x group} + e_{ti}$$

Where:
t = Time identifier (0=baseline, 1=followup1, 2=followup2, 3= followup3)
i = Patient identifier
group = 0 for patients assigned to UC and 1 for patients assigned to SC
cov = a covariate, e.g. hearing level or tinnitus severity at baseline, age, gender, education, duration of complaints (see table 4) (the actual model contained multiple covariates and covariate by time effects)
followup1 = 1 if t = 1 and 0 if else (see footnote 2 in section statistical analysis, treatment outcome), and likewise for followup2 (=1 if t=2 and 0 else) and follow-up 3 (= 1 if t=3 and 0 else)
time = Time-variable replacing time dummies (coded 0011 for the HUI as outcome and 0122 for the other outcomes) to model group by time interaction parsimoniously (see footnote c and d)
med = Mediator (time-dependent or within-subject covariate)
med x time = mediator by time interaction term
Dmed = Mediator as measured the preceding time point (to capture delayed mediation)
Dmed x Time = mediator by time interaction for delayed mediation
mod = moderator (coded 0011 for patients who received step2 care after t=1 and coded 0000 for all other patients)
med x mod = mediator by moderator interaction

e_{ti} = The random effect of patient i at time point t

With the following interpretation:

β_0 = The mean baseline in group 0 (UC)

β_1 = The mean baseline difference between groups (SC-UC) , expected to be zero due to the randomisation

β_2 = The association between the specific covariate and the outcome at baseline

β_3 = The mean change from baseline to follow up 1 (3 months after baseline) within patients who score 0 on all predictors included in the final model (e.g. group = UC, Gender = male, mean score on covariates), and likewise for β_4 (change from baseline to follow up 2) and β_5 (change from baseline to follow up 3)

β_6 = The group difference (SC-UC) in mean change from baseline to follow up 1 (3 months after baseline), which is also the group difference at follow up 1 since there is no difference at baseline, and likewise for β_7 (group difference in change from baseline to follow up 2) and β_8 (group difference in change from baseline to follow up 3)

β_9 = The effect of a specific covariate on the change from baseline to follow up 1 in both treatment conditions, and likewise for β_{10} (covariate effect on change from baseline to follow up 2) and β_{11} (covariate effect on change from baseline to follow up 3). The 3 time-dummies were replaced by a single time variable coded 0011 for the HUI and 0122 for the TQ and the THI see footnote d for interpretation

B_{12} = The group difference (SC-UC) in mean change from baseline to follow up 1, 2 and 3. For the HUI no difference between group was modelled between baseline and follow up 1, with and increase to follow up 2, remaining stable to follow up 3 (coded 0011). For the TQ and the THI: an increase between baseline and follow up 1 was modelled, doubling to follow up 2, remaining stable at follow up 3 (coded 0122)

B_{13} = The effect of a specific covariate on the change from baseline to follow up 1, 2, and 3, in both treatment conditions

B_{14} = The mediator effect on the outcome if time= 0 (i.e. at baseline)

B_{15} = The extra mediator effect if time = 1, multiplied by 2 if time is 2

B_{16} = The delayed mediator effect on the outcome at t=0

B_{17} = The extra delayed mediator effect if time = 2 or 3

B_{18} = The moderator effect on the outcome if the mediator and group both have value zero (this term must be in the model to properly test the moderator by mediator effect and has no meaning of its own) No meaning, since mediator value zero does not occur, does it ?

B_{19} = The extra mediator effect if moderator = 1 (i.e. after step2 care has started)

B_{20} = The extra moderator effect if group = 1 (i.e. specialised care)

The covariate * time interactions were dropped from the model if not significant, as assessed by a likelihood ratio test.

The null hypothesis of no difference between UC and SC implies that $\beta_6 = \beta_7 = \beta_8 = 0$.. This null hypothesis was tested against the alternative of a difference between treatments at follow up 1, 2, and 3, with a likelihood ratio test, df = 3.

The null hypothesis of no difference between UC and SC at time point 1, follow up 1, and an equal difference at time points 2 and 3, follow up 2, and follow up 3, implies that $\beta_6 = 0$; and $\beta_7 = \beta_8 \neq 0$. This hypothesis was tested against the general model with beta6, beta7, beta8 unconstrained, by replacing the original groupxfollowup1, groupxfollowup2, groupxfollowup3 terms with a single term groupxtime, with time coded as 0,0,1,1. This hypotheses was confirmed for effects on the Health Utilities Index in Cima et al, 2012

The null hypothesis of linear increase in difference at the first 2 time points, follow up 1, and follow up 2, and an equal difference at follow up 3, implies that $2\beta_6 = \beta_7 = \beta_8 \neq 0$. This hypothesis was tested against the general model with beta6, beta7, beta8 unconstrained, by replacing the original groupxfollowup1, groupxfollowup2, groupxfollowup3 terms with a single term groupxtime, with time coded as 0,1,2,2. This hypothesis was confirmed for effects on Tinnitus Questionnaire, Tinnitus Handicap Inventory, Hospital Anxiety and Depression Scale, Fear of Tinnitus Questionnaire and Tinnitus Catastrophising Scale, in Cima et al, 2012. The 4 random effects (e_{1i}, e_{2i}, e_{3i}, e_{4i}) were assumed to be multivariate normally distributed with an unspecified covariance matrix, which is the most general covariance structure.

CHAPTER IX

GENERAL DISCUSSION

Theoretical framework for the present thesis

Tinnitus Aurium, the ringing of the ears, is often defined as the perception of a continuous sound, perceivable only by the person reporting it, not generated in the external environment. Residing within and confined to the individual's subjective and perceptual experience, tinnitus is not measurable or quantifiable by objective physical recordings, and is furthermore not traceable to disease, injury, or pathology in the brain or elsewhere. By this definition, tinnitus is in itself not bothersome or physically harmful. On the other hand, tinnitus continues to tenaciously haunt patients up to the point where it interferes with every aspect of their daily living, and might therefore be considered harmful and bothersome to some. Since a definition of the instance of a bothersome tinnitus is missing, an extension to the initial definition to include an explanation for chronic tinnitus suffering might be formulated as follows:

Bothersome tinnitus is a negative emotional an auditory experience, associated with or described in terms of actual or potential bodily or psychological harm

Theories about the nature and cause of tinnitus suffering have been developed, as have been treatment and management approaches as to attenuate the problem. We can divide these frameworks according to their focal point of study, which is either the sound, i.e. the actual acoustic perception of the sound, or the suffering caused by it, i.e. the impact the sound has on the individual. Current treatment approaches roughly follow these two lines, either placing emphasis on aiming treatment at alleviating the perceptional experience by masking it (partly or completely) for habituation or soothing purposes, even to eliminate the sound altogether, or aimed mainly at decreasing the negative emotional reactions and distress resulting from it. Although it seems that we still follow the same lines of reasoning our predecessors did, current theoretical frameworks have been explanatory on some level, and the resulting treatment approaches have alleviated complaints leading to reports of occasional recovery to a satisfactory daily life in some patients. However, despite these advances tinnitus remains a disabling a condition for many.

Both of these approaches have provided the framework for the present findings, in particular two specific theoretical frameworks: the neurophysiological model of tinnitus distress and a cognitive-behavioral account both will be presented and discussed below. The main results of this thesis will be presented subsequently, followed by an integrative discussion. At the end of this chapter, theoretical and practical implications, of the present findings will be discussed. Lastly, limitations and directions for further research will be provided.

The Neurophysiological model

An influential and widely adopted theory explaining tinnitus and tinnitus-related complaints, leading to almost all of today's sound-based approaches, has been the neurophysiological model (NP model) of tinnitus distress introduced by Pawel J. Jastreboff (Jastreboff, 1990). The main premise of this model is that the actual source (the tinnitus sound) is not causing the annoyance, it is the subjective experience of the individual which will determine whether this sound is experienced as aversive or not. Interestingly, Jastreboff provides a cognitive account by this main premise. According to Jastreboff, the NP model is specifically based on the following learning principles; conditioned fearful responses (conditioned reactions) elicited by the tinnitus sound, are the cause of the tinnitus becoming bothersome (see figure 1). This line of reasoning stems from a series of behavioural animal experiments, in which classical and operant conditioning paradigms were used to induce tinnitus-like fearful behaviour in rats (Jastreboff, Brennan, Coleman, & Sasaki, 1988; Jastreboff, Brennan, & Sasaki, 1988). The NP model distinguishes 3 stages:

1. The generation of the auditory stimulus usually occurs in the auditory periphery, i.e. as a result of a disorder in the cochlea or the cochlear nerve, though more central generation, i.e. in sub-cortical structures of the brain, might occur as well.
2. The detection of the tinnitus-related signal (tinnitus sound), against the background of other neuronal activity, in sub-cortical auditory regions, as a result of pattern recognition.

3. The perception and evaluation of this auditory stimulus in cortical areas (auditory and others), and the sustained activation of the limbic (emotional) and autonomic nervous system, both sub cortical.

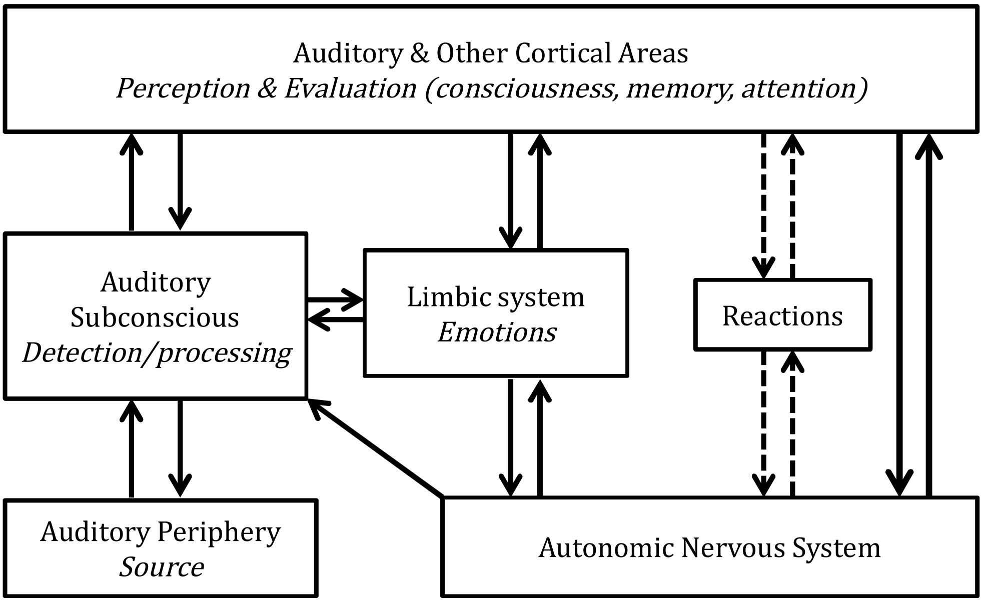

FIGURE 1. THE NEUROPHYSIOLOGICAL MODEL OF TINNITUS ADAPTED FROM (JASTREBOFF, 1999), AND REPRODUCED WITH THE PERMISSION OF THE AUTHOR.

The classical learning paradigm in the animal model of tinnitus (Jastreboff, Brennan, & Sasaki, 1988; Jastreboff, Hazell, & Graham, 1994; Jastreboff & Sasaki, 1994; Ruttiger, Ciuffani, Zenner, & Knipper, 2003) has not been translated to the NP model of tinnitus distress in humans so far. Presently, the learning principles that could explain the NP models predictions are hypothesized below and depicted in figure 3.

The NP model predicts that the last stage (3) plays a key role in the severity of tinnitus. It purports that emotions dictate the level of annoyance the tinnitus induces, that is, when negative reactions are not associated with the source, the person only experiences a sound to be continuously present, but without being annoyed by it.

If we hypothesize these NP-model predictions in terms of a classical learning-paradigm, it follows that we can define the aversive tinnitus experience (US) as the tinnitus-sound coinciding with the negative physiological and emotional reactions, or the unconditioned-response experience (UR). The neutral tinnitus signal, not associated with these negative sympathetic-/physiological/emotional reactions, represents the conditioned stimulus (CS). The contingent pairing of the CS and the US, allows the CS to become a predictor of the US (the aversive tinnitus experience), and in turn elicits negative conditioned responses (CR), such as cognitive misattributions and fearful responses. See figure 3 for a schematic representation.

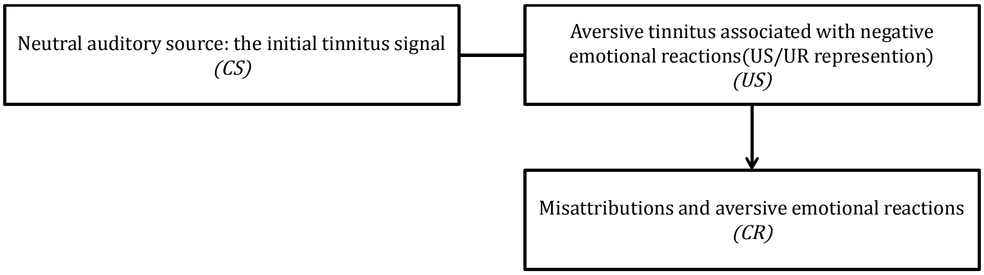

FIGURE 2. SCHEMATIC DEPICTION OF THE CLASSICAL CONDITIONING PRINCIPLES IN THE NP MODEL AND THE TRT APPROACH

The treatment stemming from the NP-model's theoretical framework is called Tinnitus Retraining Therapy (TRT) (Jastreboff & Jastreboff, 2000). TRT consists of two elements: the first main treatment element is called cognitive restructuring, that is 'retrain thinking' of patients by directive counselling (Jastreboff & Hazell, 1993). This part aims to alter the interpretation of the tinnitus signal, purporting that the evaluation ('negative emotional reactions and conditioned responses') of the sound changes as a result (stage 3). If we describe this process in classical learning terms, we could say that this TRT treatment element aims at a re-evaluation of the US, attenuating the US's negative valence to a more neutral one. The second treatment element is aimed at the sound detection level (stage 2). The model purports that the abnormal pattern recognition process of tinnitus can be reversed by exposing patients to white noise (by means of ear level devices) for long periods of time (12 to 18 months), since that would eventually interfere with the tinnitus pattern and lead to automatic habituation. According to the theory, tinnitus should not be masked completely, but attenuated when wearing these sound generating devices. The main aim of TRT is to retrain the cortical and subcortical structures of the brain which are involved in the higher order processing of the tinnitus signal (stage 3), as opposed to changing the signal on the perceptional level or suppressing the generation of the tinnitus (Stage 1), i.e. the CS remains unchanged.

From a classical learning perspective, TRT masking procedures might be aimed at 1) counterconditioning; the pairing of the CS (the tinnitus signal) with a different and opposing US (the neutral 'soothing' masking sound, not eliciting simultaneous negative physiological and emotional reactions), or 2) a discrimination/generalization training; a continuous different signal (the masking sound), similar to the CS (the neutral tinnitus signal), which is not paired with the US, will therefore not lead to the conditioned reactions. After repeated exposure to this masking sound, the conditioned response to this masking signal will generalize towards the CS, which than in turn no longer elicits negative emotional reactions.

Furthermore, according to the neurophysiological approach, in order to successfully retrain the brain to habituate to the tinnitus signal, it should be perceivable at all times while exposed to the white noise. This might indicate that the masking procedure is a form of 3) exposure to the CS, in that it aims to expose patients to the tinnitus signal, though attenuated by masking. This will enable patients to experience the CS without always eliciting the US, because of the soothing effect of the masking. Therefore the CS will be de-paired with the US, leading to the eventual extinction of the US.

It remains unclear at which of these learning theory mechanisms the masking procedures are aimed, since the purported masking-effects in decreasing tinnitus distress are explained in terms of neurophysiological mechanisms in the NP model.

In sum, the theory predicts that on the sound generating level (stage 1) no changes will occur, the tinnitus signal (CS) will remain the same over time in loudness and intensity. In fact, it is hypothesized that as a result of this TRT bottom-up approach, the resulting changes in the interpretation and negative evaluation (US) will be generated automatically, and in turn results in diminished tinnitus complaints. The theory predicts that the strength of the functional connections between the tinnitus signal and the emotional reactions will change as a result of TRT; in other words the main aim is to recondition the tinnitus signal, changing the valence of the signal from negative to neutral. Robust evidence for the effectiveness of this treatment approach has remained elusive (Hoare, Stacey, & Hall, 2010; Hobson, Chisholm, & El Refaie, 2010; Phillips & McFerran, 2010), though the TRT cognitive treatment element has been found to be of benefit (Henry, et al., 2007; Henry, Schechter, Nagler, & Fausti, 2002; Henry, et al., 2006; Kroner-Herwig, Frenzel, Fritsche, Schilkowsky, & Esser, 2003; Zachriat & Kroner-Herwig, 2004).

Why the evidence for the benefit of TRT has remained unresolved might be related to the lack of specificity of the [learning] mechanisms that are involved during sound masking-procedures. The aims of TRT are specified in general neurophysiological processes only. Masking-procedures might have influenced several different learning mechanisms, e.g. those hypothesized above, leading to either unintentional or undiscovered effects, or even to opposing effects, cancelling each other out in the process. In order to gain insight into the effects of masking the tinnitus-signal, experimentation is necessary to further explore the classic conditioning paradigm the NP model is based on, and to test the specific hypotheses regarding the different hypotheses regarding these learning mechanisms. Unfortunately, experimental studies thus far have been focussed on animal models, and have not been aimed at dismantling these mechanisms in the human model (Brozoski, Wisner, Sybert, & Bauer, 2012; Jastreboff, Brennan, Coleman, et al., 1988; Jastreboff, Brennan, & Sasaki, 1988). Moreover, studies thus far have relied on conceptually hybrid and non-specific outcome measure, possibly insufficiently sensitive to measure the effects on these learning mechanisms. As has been mentioned before, the low methodological quality of investigations, leading to ambiguous results, in the past has not aided in increasing the level of clinical evidence for the masking element of TRT, or for the cognitive TRT element for that matter. The cognitive element of TRT is however aimed specifically at the mis-interpretation of the signal, or at a re-evaluation of the US, in order to decrease the negative emotional responses. It has been repeatedly observed that negative emotional responses explain a large part of general tinnitus distress (Cima, Vlaeyen, Maes, Joore, & Anteunis, 2011; Henry, Jastreboff, Jastreboff, Schechter, & Fausti, 2002; Henry, et al., 2006; Henry & Wilson, 1995; Herraiz, Hernandez, Plaza, & Santos, 2005; Hesser & Andersson, 2009; Kleinstauber, et al., 2012; Langguth, Kleinjung, & Landgrebe, 2011; Sweetow, 1986; Westin, Ostergren, & Andersson, 2008), clinical benefits might therefore become more apparent on the instruments which are currently available. The mechanisms of change underlying these cognitive effects remain nonetheless unresolved as well.

A cognitive-behavioural account; the fear-avoidance model

Since consensus exists that tinnitus suffering is mostly defined by its psychological impact on patients, a second line of reasoning and investigations came from cognitive psychology (Hallam, Jakes, & Hinchcliffe, 1988; Hallam, Rachman, & Hinchcliffe, 1984; Sweetow, 1986). The cognitive account from Hallam (Hallam, et al., 1984) and the cognitive tinnitus sensitization model proposed by Zenner and Zalaman (Zenner & Zalaman, 2004) provided a psychological explanation for the chronic nature of tinnitus complaints. Processes of mis-interpretation, increased attention, negative affective reactions, and inadequate coping towards the tinnitus were distinguished, and led to the implementation of cognitive behavioural treatments (CBT) for tinnitus patients (Andersson, 2002; Henry & Wilson, 1996; Sweetow, 1995). Evidence that a CBT approach is beneficial has been accumulating (Hesser, Weise, Westin, & Andersson, 2011; Hoare, Kowalkowski, Kang, & Hall, 2011; Martinez-Devesa, Perera, Theodoulou, & Waddell, 2010), however, the associations between these cognitive behavioural processes are as of yet not specified in a single theoretical framework. A framework possibly providing a cognitive-behavioural account for tinnitus is based upon a cognitive-behavioural model for chronic pain. The parallels between chronic tinnitus and chronic pain have been suggested earlier (Folmer, Griest, & Martin, 2001; Isaacson, Moyer, Schuler, & Blackall, 2003; Jastreboff, 1990; Moller, 1997, 2000; Tonndorf, 1987).

The Fear-Avoidance (FA) model for chronic pain (Lethem, Slade, Troup, & Bentley, 1983; Vlaeyen & Linton, 2000, 2012) includes above-mentioned processes and combines them in a theoretical model depicted in figure 3. The FA model predicts that individuals, when injured, are subject to automatic emotional and sympathetic responses. If pain persists, threatening situations, signalling pain or (re) injury, through classical conditioning, elicit conditioned fear responses such as increased arousal, hypervigilance, and eventually avoidance/escape behaviours. These behaviours become negatively reinforced through instant diminishing fear, which is adaptive in the acute phase. However, in the long run, when pain persists and medical curative efforts are ineffective, heightened fear is maintained. Through maintained fear and avoidance behaviours, the increased functional disability, and co-occurring depressive mood and general anxiousness, results in chronic pain disorder.

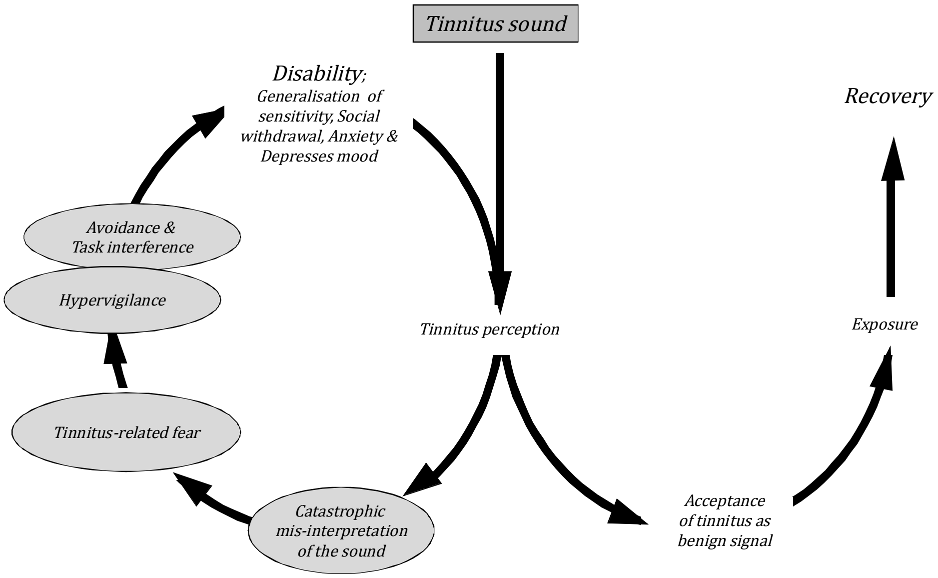

FIGURE 3. A FEAR-AVOIDANCE MODEL FOR CHRONIC TINNITUS, ADAPTED FROM THE FEAR-AVOIDANCE MODEL OF CHRONIC PAIN (VLAEYEN & LINTON, 2000).

Following the two lines of past research and theoretical reasoning, first by hypothesizing that conditioned negative responses are the main cause of the suffering (Jastreboff & Jastreboff, 2006), and that these aversive responses towards the tinnitus sound lead to misinterpretations, fear-responses, and maintained tinnitus distress in the long run (Andersson & Westin, 2008), the FA model could combine these principles into a new framework, adding a behavioural compound, and shedding light into how these mechanisms are associated. It is therefore that this fear-avoidance approach has presently been applied to chronic suffering; both to discover new venues for investigations, as well as to develop a novel CBT based tinnitus treatment approach.

Similarities between the models

It can be argued that both the NP and the FA model are based on the premise that a neutral signal can receive a negative valence by classical conditioning, in which an individual learns that a neutral signal becomes predictive for negative states as a result of automatic negative responses elicited by the neutral signal (Jastreboff & Jastreboff, 2006; Vlaeyen & Linton, 2000). Both models purport also that these aversive responses could lead to misinterpretations or negative evaluations, in turn leading to fearful-responses (emotional and attentional) and even behaviours, explaining maintained tinnitus distress in the long run (Andersson & Westin, 2008). This latter premise is based on an operant component in learning theory terms and remains unexplained in the NP model, whereas the FA model provides specific predictions on this level, which leads us to the main difference between the models.

Differences between the models

Whereas the NP model is mainly a model of tinnitus generation and detection, the FA model is predictive beyond that, and picks up there where the NP model stops being explanatory. The main conceptual overlap might lay in the beginning of both models just until the detection/perception and interpretation level, and the classical learning principles, as described above. They differ in explaining how these learning principles, specifically the operant part, play a role. The NP model in mainly based on neurophysiological processes, with attempts to explain these in neurophysiological mechanisms, as a result providing explanations in classical or operant conditioning mechanisms in general terms. The opposite holds for the FA model which is based on learning theory principles, and explanatory predictions about both the classical, but moreover the behavioural (operant) mechanisms. These differences might lead to different predictions and therefore also to different treatment strategies.

Strengths and drawbacks of the NP and the FA models

The NP model has several strengths in that it has offered an animal model of tinnitus complaints. The model has provided a means to study behavioural and neurophysiological mechanisms, which are not always possible in human research. Moreover, the model has important merits in providing patients and physicians with a comprehensive explanation of the origins and generation of the chronic bothersome tinnitus complaints, which for most patients has remained an unresolved mystery and has exacerbated frustration in many. The NP model is a model of tinnitus generation and detection; it offers an explanation about the onset of acute tinnitus. The main premise of the model is that the tinnitus percept is caused by malfunctions in the cochlea, and that the central nervous system tries to compensate for this change by increasing sensitivity in processing auditory input, leading to new patterns and the fine-tuning of attentional processes. Since this explanation does not offer predictions about when tinnitus becomes a nuisance and when not, cognitive and emotional processes are included in the model as well. The main drawback of the NP model is that the latter processes are described in very general terms and remain vague and unspecific in explaining tinnitus-related processing, which holds in particular in describing the 'reactions' (sic), as a result of cognitive and emotional processes. Moreover, the specific classical conditioning principles which explain chronic tinnitus distress are described in general terms as well. As a result, the main aims of TRT treatment elements stemming from this model remain unclear. Predictions about how these cognitive, emotional and behavioural processes are associated, how these could be explained in classical and operant conditioning terms, and why they should be targeted in treatment are lacking in this model.

A particular strength of the FA model is that it provides predictions about tinnitus-specific cognitive, emotional and behavioural mechanisms possibly explaining how tinnitus becomes bothersome in some, but not all. As it is based on learning theory principles it offers predictions about classical and operant mechanisms, and thereby giving more specific directions for treatment. In addition, this approach has proven its merits in chronic pain research already. However, one could argue that in this model the mechanisms leading to the onset or generation of the tinnitus are lacking. Moreover, the question as to why some, but not definitely not all, tinnitus perceiving individuals have catastrophic tinnitus-misinterpretations, leading to this self-perpetuating circle of fear-avoidance and disability, remains unexplained as well. Tinnitus is not painful, that is, in the experience of pain, the consequential physical and emotional reactions might lead or contribute differently to chronic disability, than they do in the experience of a sound, without an external source, specifically in the transition from acute to chronic suffering. In most cases, acute pain is bothersome to everybody, although that is in part dependent upon the context of this pain. It might even be argued that when confronted with acute pain, we all tend to interpret this signal negatively. This cannot be stated so unequivocally about perceiving an internal sound. The question as to why the initial tinnitus signal is interpreted negatively by only a small part of the tinnitus-perceiving individuals might be of importance and remains as of yet unanswered.

Main findings

The review in Chapter 1 revealed that current treatment approaches in tinnitus management are highly diverse, consist of combinations of different treatment elements, and tinnitus diagnostics and outcome assessments differ widely, not only across investigations, but as well across treatment approaches, and clinical settings. The lack of a standard diagnostic algorithm and therefore heterogeneous outcomes of the included studies lead to challenges in interpretability and comparability. Moreover, the low methodological quality of most studies revealed relatively low levels of evidence for the benefits of any of the investigated approaches. It was concluded that an overall CBT based approach was recommended, since evidence for this approach seems most promising. The evidence for the benefits of therapy elements aimed at the sound perception level is modest at best. A last important observation is that little is known about the processes of change as a result of treatment. Important mediators, explaining why treatment is beneficial or not, and moderators, providing information about what is beneficial for whom, remain to be discovered.

Tinnitus is a subjective experience and therefore difficult to measure and quantify, and several tinnitus measures for the assessment of the impact of tinnitus on cognitive, emotional, physical, and auditory functioning, have been developed over time. The most frequently used measures for tinnitus distress are the tinnitus questionnaire (TQ) and the tinnitus handicap inventory (THI). Although both have their merits, they are also conceptually hybrid in that they assess a combination of different constructs at the same time. They are therefore unfit for investigating the associations between these constructs. A valid and reliable measure to assess more general functional disability, i.e. the interference of tinnitus with performance on major daily life activities, was lacking. A first psychometric examination, as described in Chapter 2, supported that the Tinnitus Disability index (TDI), introduced as a novel unitary brief index, is a valid measure for assessing tinnitus-related disability in daily life. The TDI was found to be a brief and easily administered index, with good test retest reliability, capturing a unitary construct, namely tinnitus disability. Tinnitus intensity, poor general health, and tinnitus severity were found to be significantly associated with higher ratings of tinnitus disability, though the relatively low correlations suggest that tinnitus disability as measured with the TDI is conceptually distinct from these other tinnitus related constructs, and that it seems to measure a unique underlying construct. Given that the TDI is a newly developed assessment instrument, more work is needed not only in the replication of these first findings, but also in establishing norms, such that for each individual a meaningful level of disability can be identified. A recent and promising method is based on regression models. This approach offers at least 2 advantages. First, multiple regression allows determination of patient-variables which are and which are not relevant to the norming (validity). Second, by using information from the entire sample, multiple regression leads to continuous and more stable norms for any subgroup defined in terms of prognostic variables (reliability) (Van Breukelen & Vlaeyen, 2005).

The FA model of pain provided directions in predictions about the role of perceived threat value, cognitive misinterpretations, and tinnitus-related fear responses, and whether these influence tinnitus disability. Chapter 3 describes a cross-sectional study in which the level of catastrophizing was found to be associated with both self-reported tinnitus-specific fear and increased attention towards the tinnitus. Higher levels of tinnitus-related fear in turn were associated with increased attention towards the tinnitus. Finally, catastrophic misinterpretations of tinnitus were significantly related to poorer quality of life ratings. Heightened fear uniquely added to this model, above and beyond the contribution of catastrophizing about tinnitus, suggesting that tinnitus-related fear fully mediates the association between tinnitus catastrophizing and quality of life.

Based on the two theoretical frameworks described earlier, the NP model and the FA model, a novel stepped-care CBT based tinnitus treatment, including counselling elements from TRT in the initial step, was developed and evaluated (Chapters 4 and 5). The first step of the experimental CBT based treatment included, next to audiological diagnostics and education, extensive CBT-based psycho-education and psychological analysis and advice. Step 1 was aimed at educating patients about the cause, nature, and mechanisms of chronic tinnitus, in order to decrease mis-conceptions about possible harmfulness of the sound. The NP model served as the framework, and the main therapeutic approach in this initial step was aimed at cognitive restructuring accordingly. A second aim was to assess the impact of the tinnitus on patient's cognitions, emotions and behaviour, and to provide additional education with use of the fear-avoidance framework. A third aim was to assess whether this initial step was sufficient or whether an additional intervention step was indicated. The second step consisted of cognitive behavioural therapy in group format, aimed at the constituents of the FA model, including behavioural techniques, extending beyond the NP model and the TRT approach. Step 2 aimed at increasing patients understanding of cognitive mis-attributions, decreasing tinnitus-related fears and avoidance behaviour, increasing the awareness of these mechanisms, and stress reduction in general. Therapy included first, education and applied relaxation, for decreasing the perceived harmfulness of the tinnitus signal, decreasing fearful responses and stressful states. Additionally, patients were exposed to their tinnitus sound, tinnitus- promoting situations, and the resulting negative reactions, in order for the extinction of tinnitus-related fear to occur and re-evaluate the meaning of (initially) aversive tinnitus sound. Acceptance and commitment therapy elements as well as mindfulness-based approaches were included to decrease experiential avoidance. Last, counseling on daily activity structuring, sleep patterns, inter-personal relations, communication, and implementing techniques in daily life were provided in themed group-sessions, aimed at the generalization of skills towards daily life functioning. The effectiveness of this new CBT-based tinnitus-treatment protocol was investigated in a large RCT, including 492 participants. Since the evidence for sound-based therapy, or masking procedures, is poor, these TRT components were not included in this novel treatment approach.

Results demonstrated that specialised CBT-based tinnitus treatment (SC), organized in two consecutive steps, combining the counselling elements of TRT within an overall CBT-framework, is more effective than the care that is usually provided throughout the Netherlands (UC). The usual care consists of mainly audiological diagnostics and rehabilitation aimed at the sound-perception level by ear-level devices (hearing aids and sound-generators). Specialised care (SC) as opposed to care as usual (UC) led to increased health-related quality of life, and reduced tinnitus-severity and tinnitus impairment. Additionally, SC compared to UC generated greater improvements in general negative emotional states, and decreased level of tinnitus-related catastrophic thinking and tinnitus-related fear. The effectiveness of SC as compared to UC was demonstrated not only after the first 3 months of step-1 treatment, but also after the additional, and more intensive step-2 treatment, as well as after 4 months of a no-treatment follow-up period. Furthermore, mild and severe tinnitus sufferers, as measured with the Tinnitus Questionnaire at baseline, appeared to benefit equally from getting SC treatment, instead of UC treatment. These findings support our main hypothesis that a CBT based stepped care approach with elements from TRT, is effective in tinnitus management, both for milder forms of tinnitus suffering as well as for more severe tinnitus incapacitation. Finally, the largest group of patients were effectively treated within a fairly short period of time, since patients with mild tinnitus complaints, receiving step-1 treatment only, were included in all analyses, and effectiveness of SC was established throughout the whole group.

Results from the outcome study of the CBT-based approach indicate that a stepped care approach, allocating additional resources only when needed most, is most beneficial, and moreover, could be more cost-effective. In Chapter 6, a subsequent extensive economic evaluation, conducted from a societal perspective supported the cost-effectiveness of the stepped-care CBT-based approach. Although costs associated with the tinnitus-care in the treatment centre were considerably higher in the SC, as opposed to the UC, this was partly compensated by lower costs for tinnitus-related health-care outside the treatment centre in the SC. Costs of productivity loss were higher in SC as well. Considering the societal costs of SC per gained quality-adjusted life year (QALY), and the low quality of life scores at baseline, indicating the relatively high burden of tinnitus, the conclusion that the SC treatment is cost-effective seems justified.

As a first step in answering the question as to what could increase effectiveness of this CBT based approach, and to refine future treatment, a further investigation into the mechanisms of change as a result of this treatment was conducted and described in Chapter 7. In line with the fear-avoidance model predictions, and the cross-sectional study described in Chapter 4, tinnitus-related fear was found to mediate the benefits of a CBT based approach in specialized tinnitus treatment (SC) not only on quality of life and tinnitus severity, but on tinnitus-related disability as well, when compared to usual audiological intervention (UC). Post-hoc analyses of the data from the RCT revealed that patients in the specialised treatment group were significantly less disturbed by their tinnitus, as a result of decreased tinnitus-related fear. These findings corroborate the notion that CBT has an attenuating effect on fear and fear related behaviours, thereby decreasing tinnitus complaints.

Integrative discussion and implications of the main findings

Evidence for the effectiveness of curative tinnitus treatments has, as of yet, not been established. Whether surgical interventions, drug therapy, or neurological brain stimulation, (Elgoyhen & Langguth, 2010; Langguth & Elgoyhen, 2012; Meng, Liu, Zheng, & Phillips, 2011), results indicate benefits to be absent, very minor, or particular to a very small sub group of patients. As a result, several rehabilitative protocols and treatment avenues have been introduced over the past 30 years, and positive reports have been described. However, reviews of past research have all similarly concluded that the available evidence has been too weak and not convincing enough to reach sound conclusions about what treatment approach is beneficial for which patients. Evidence exists for a CBT approach, although the effects are moderate, and empirical evidence for the use of hearing aids, sound generators, sound based therapies, and TRT is still lacking. Ironically, and despite their weak empirical support, sound-based approaches are still is the most widely used treatment approach today (Hoare, Gander, Collins, Smith, & Hall, 2012; Hoare & Hall, 2011).

The lack of a standard diagnostic or treatment outcome heuristic has complicated the interpretation and comparison of past research findings. The Tinnitus Handicap inventory (THI) (Newman, Jacobson, & Spitzer, 1996), and the Tinnitus Questionnaire (TQ) (Hallam, et al., 1988; Meeus, Blaivie, & Van de Heyning, 2007) are two of the most commonly used for clinical purposes as well as for research outcomes. A new promising measure is the Tinnitus Functional Index (Meikle, et al., 2012), which has been recently added to the list of tinnitus treatment outcome measures. Though these are viable instruments, in that they are able to assess tinnitus suffering and improvement reliably, and have good psychometric properties in different languages, they also are conceptually hybrid in that they measure different constructs simultaneously. The Tinnitus Disability Index (TDI), as presented in the present thesis, may constitute a valuable addition to these commendable tools. Since it seems to be a unitary measure for assessing the impact of tinnitus on daily life activities, it could be used as a reliable outcome when, for example, investigating mechanisms of change in order to disentangle known associated factors, such as cognitive misinterpretations and fearful responses, and specifically how they interplay and contribute to chronic tinnitus suffering.

A treatment approach based on both the NP and the FA models, the CBT based specialised treatment, was found to be effective in decreasing suffering in a large group of patients with mild as well as severe tinnitus complaints. Although the SC as a whole was based on CBT principles and aimed at decreasing misinterpretations, the threat value, and fearful responses towards the tinnitus, we still do not know which of the individual elements contributed most to the overall effectiveness, or which of the treatment ingredients are most beneficial for whom. Post hoc analyses supported the importance of addressing tinnitus-related fear and fear-responses in the management of patients with disabling tinnitus. This finding also supports the conjecture that initial fearful responses towards the tinnitus sound, and possibly as a result safety behaviours, lead to more severe problems in the long run, not only decreasing chances for tinnitus habituation, but also maintaining the tinnitus impairment as such. In that case, the FA model and the proposed association between its constituents may apply to chronic tinnitus as well.

The predictive value of these relatively new concepts on disability, i.e. tinnitus related mis-interpretations and tinnitus related fear, have been investigated in chronic pain suffering as well, and findings indicate that these indeed are of importance in chronic pain (Crombez, Vlaeyen, Heuts, & Lysens, 1999; Gheldof, et al., 2010; Jensen, Karpatschof, Labriola, & Albertsen, 2010; Leeuw, et al., 2007). It has been demonstrated that pain-related fear is strongly associated with pain severity, disability, physical performance, daily functioning, and even work-related disability -sickness and -loss (Asmundson, Norton, & Allerdings, 1997; Crombez, et al., 1999; Dawson, Schluter, Hodges, Stewart, & Turner, 2011; de Jong, et al., 2005; den Hollander, et al., 2010; Gheldof, et al., 2010). Moreover, recent evidence seems to indicate that pain-related fear acts as a mediator between pain severity, intensity, negative mood and pain disability (Gheldof, et al., 2006; Kamper, et al., 2012; Meulders, Vansteenwegen, & Vlaeyen, 2012). On the other hand, one of the assumptions of the NP model (Jastreboff, 1990; Jastreboff & Hazell, 1993; Jastreboff & Hazell, 2004), is that conditioned reflexes in processing the tinnitus sound are especially important and that the perception and interpretation of the signal is strongly related to heightened negative emotional states, eliciting increased attention towards the tinnitus, enhancing the perception itself (Jastreboff, 1990). This is in accordance with the FA model, which expands on these notions and incorporates a possible cognitive-behavioural account for the onset and maintenance of chronic bothersome tinnitus. Our results so far do not contradict the NP model, and provide support for the FA model, and if tinnitus-related cognitive misinterpretations and fear are of importance, we might assume that consequentially, ineffective safety behaviours are as well (Blaesing & Kroener-Herwig, 2012). Tinnitus-related safety behaviours are likely to be of experiential nature, based on the fear of or the unwillingness to hear, be aware of, and even think about the tinnitus, leading to avoiding silent (or tinnitus provoking) environments, avoiding restful states and continuously searching for distraction in either physical or mental activity. Treatments specifically aimed at these factors might effectively decrease the impact of tinnitus in daily life. Extending the NP model as to include a cognitive behavioural account, might be helpful as well in uniting treatment approaches, which seem to have been largely divided into opposing treatment avenues. Taking a more integrative approach in clinical practice as well as in research might lead to more effective assessment and management of disabling tinnitus.

Limitations of present findings and directions for future research

New concepts, possibly explaining the extended suffering of tinnitus patients, have been introduced and investigated. Whereas a systematic review of the current state of evidence for multidisciplinary treatments served as a starting point of present investigations, given the similarities between tinnitus and chronic pain, we formulated most hypotheses, regarding the psychological mechanisms underlying chronic tinnitus, based on findings in the chronic pain literature. A number of limitations have to be considered, and these will be summarized first below, last, directions for future investigations will be presented.

Limitations

The review of literature showed that previous studies are difficult to compare, low in methodological quality, and therefore with low levels of evidence.

Current treatment approaches in tinnitus management are as a result highly diverse, combine several treatment elements, and standard tinnitus diagnostics or outcome assessments are lacking across research areas, clinical settings, and countries. Although CBT for tinnitus seems the most promising approach, it is difficult to interpret previous data and reach sound conclusions about what tinnitus treatment approach is effective for whom.

The TDI, a novel measure to assess how much impact the tinnitus has on daily life activities, was found to have good psychometric qualities, and seemed robust. However, these results were based on a web-based assessment, which might have created a selection bias in that a group of tinnitus patients might have been left out. Furthermore, the study was carried out in a Dutch speaking population only, and the psychometric quality of the TDI in other languages remains to be established. Since these results concern cross-sectional data, we have not yet been able to confirm whether it is sensitive enough to measure changes over time or as a result of intervention, and norms for the interpretation scores of patients on the TDI, are still missing.

Given the similarities between tinnitus and chronic pain, we formulated a number of hypotheses regarding the role of fear of tinnitus, catastrophic mis-interpretations, and increased awareness, based on findings in the chronic pain literature. In a first cross-sectional study the theoretical validity of the FA model was tested in a group of tinnitus patients. Though results suggest that the FA model might be applicable in chronic tinnitus as well, we have to keep in mind that the novel measures were initially developed for chronic pain research. That is, specific tinnitus-related items might be missing from the current measures, or included items might be in need of fine-tuning to fit tinnitus complaints more adequately. Furthermore, results concerned cross-sectional data and causality cannot be inferred as of yet. Finally, audiological factors, such as level and lateralization of hearing loss, tinnitus localization and psycho-acoustic measures such as frequency and intensity, were not available for these analyses.

When preparing for the RCT and developing the research protocol, difficulties were found in determining standard usual care for tinnitus in the audiological centres across the Netherlands. Therefore a telephone survey was conducted amongst all audiological centres, and usual tinnitus care was modelled for investigation purposes. This implicates that at present, the implemented form of usual care was standardized, whereas in reality, clinical variation in treatment in usual care practice is large.

The specialised CBT approach seems very promising; however, it was a combination of different treatments elements; TRT counselling, group educational counselling, individual psychological counselling and group-wise CBT treatments. The step-2 CBT group treatments in turn consisted of different CBT elements, including first education and applied relaxation, second, exposure towards tinnitus (and resulting negative emotional reactions) as to augment long-term habituation, and ACT and mindfulness based elements to decrease experiential avoidance, and last counselling on daily-structure, sleep patterns, relations, communication, and implementing techniques in daily life. SC was thus an amalgamation of diverse treatment elements, leaving the question which of these elements was most beneficial for whom, and why, unanswered. For example, it has been suggested that TRT as an additional treatment approach to CBT has no additional beneficial effects (Hiller & Haerkötter, 2005). Additionally, since this approach consists of different elements, a specialised multidisciplinary team is needed, working integrally. The implementation across the different clinical settings and across countries might lead to new difficulties as these are all differently restricted in resources. Information is needed on what are the most effective treatment elements, and what elements are of less additional value, in order to fine-tune current treatment strategies. Moreover, the dismantling of the present treatment could lead to a differentiation in treatment strategy to better suit different subgroups of patients. The dismantling and tailoring of the treatment might lead to better implementation strategies as well, leading to allocation of the treatment elements to the appropriate settings.

In the main analyses of the economic evaluation, the intention-to-treat method was abandoned, and because of the missing data and non-responses, multiple imputation of data was employed. The proportion of missing data and non-response was larger than expected, and the possibility of non-random causes for dropout cannot be ruled out. Though the analyses were repeated with predicted values of the outcome from the intention-to-treat analyses, supporting the outcomes in the main analyses, and supporting that the SC treatment approach is cost-effective, the uncertainty surrounding the incremental costs and effects are considered to be large. Additionally, the present time horizon of 12 months is fairly short. A longer time horizon is necessary to identify relevant longer-term outcomes; especially since quality of life slightly improves at the last follow-up in the SC, and deteriorates in the

UC. A longer time horizon would provide insight into whether the more favourable results for the SC are robust over time.

A post-hoc analysis of the data suggested that tinnitus-related fear plays a mediating role in the benefits of a CBT based approach in specialized tinnitus treatment. Caution is warranted as confounding and unmeasured factors possibly contribute to changes over time, which might be of influence on the mediator and outcomes. Interpretation of the data supporting mediation can only be done under the assumption that there are no hidden confounders affecting the mediator and the outcome simultaneously (Emsley, Dunn, & White, 2010). Furthermore, in these post-hoc moderated-mediation analyses, the intention-to-treat method was abandoned as well, meaning that analysis was based on treatment-as-obtained instead of on treatment-as-assigned, therefore results must be regarded as tentative. Evaluating data on the treatment-as-obtained principle, instead of treatment-as-randomly-assigned, poses a risk of selection bias, where undetected systematic differences between the groups were already present before the start of the experiment, posing a threat to the internal validity of current results.

Directions for future research

Tinnitus is distinct from pain

Though parallels between chronic pain and chronic tinnitus are apparent, the differences between chronic pain and chronic tinnitus are noteworthy as well. Misinterpretations, fears and behavioural responses specific to tinnitus for example, are likely to differ from those found in chronic pain. Whereas pain might be interpreted as indicative for injury at the bodily level, tinnitus might be more easily interpreted as being indicative for brain injury or malfunction, of becoming deaf, or even of ‘having a nervous breakdown’ (Hallam, et al., 1988; Hallam, et al., 1984). Most reported thoughts and beliefs in tinnitus patients are: ‘I am going insane’, ‘I will lose my hearing’, and ‘I have a tumour’. The resulting fears might differ as well, leading to different safety strategies in daily life. Indeed, we found that tinnitus disability is a unitary concept, whereas in chronic pain research specific behavioural factors interfering with daily life functioning can be discerned. For example in chronic pain, fear of movement is an important debilitating factor, leading to avoidance of specific movement related activities. In tinnitus patients these avoidance strategies might be less overt and more apparent on an internal experiential level (Hesser, et al., 2012). More in-depth research into these concepts and their assessment is warranted.

Psychometric challenges

The novel concepts of tinnitus-related mis-interpretations, increased awareness and tinnitus-related fears were introduced as well as instruments to measure them. First, additional psychometric evaluations are needed to examine the psychometric properties of instruments in larger samples of patients with tinnitus. In future studies it would be of interest to see whether these constructs are associated with tinnitus-related avoidance behaviours, as is predicted in the FA model. In a recent cross-sectional investigation it was suggested that avoidance behaviours indeed increase significantly along with levels of tinnitus handicap, and that fear-avoidance partially explained the relationship between anxiety sensitivity and the cognitive, catastrophizing dimension of tinnitus handicap (Kleinstauber, et al., 2012). Nevertheless, no causal relationships can be inferred from present data; which presents a threat to internal validity of the results. Whether there are causal relationships between catastrophising, fear, increased tinnitus awareness and disability, and moreover, the direction of these associations, remain unclear. To clarify which variable is the cause and which is the effect further experimentation is needed, in which the probable causational variables should be manipulated. Moreover, it should be investigated whether there are possible confounding variables, which are as of yet unknown.

The TDI was introduced as a robust and valid measure for assessing tinnitus related impact on daily functioning. Whether TDI is a valuable addition to existing measures depends on its sensitivity to measure changes over time, evaluate effects of interventions, and its suitability in clinical decision making. The TDI might offer a more unique unitary measure of disability in comparison to the already existing more hybrid instruments. However, more extensive evaluations of the TDI are warranted, as well as investigations into the comparability of the TDI to other new promising measures on tinnitus disability. Future research should be directed towards establishing the sensitivity of the TDI across patient groups, evaluating different interventions, and over longer periods of time. Moreover, in order to interpret the raw scores of patients and for clinical and diagnostic decision-making, norms should be established, based on the comparison to the values of scores of a relevant reference population using regression models of raw scores on demographic and other patient variables. Compared with traditional norming methods, this approach offers at least two advantages: first, it allows determination of which patient variables are relevant to the norming and which are not (validity). Second, by using information from the entire sample rather than subgroups based on gender and age, multiple regression leads to continuous and more stable norms for any subgroup that is defined in terms of prognostic variables (reliability). (Van Breukelen & Vlaeyen, 2005)

Effective treatment components

The overall effect of specialised CBT-based treatment was found to be beneficial, however, which of these elements is most beneficial for whom, or in what phase of tinnitus suffering, acute or chronic, or for what subgroup of patients, still has to be established. It is indicated that future research be focusing on dismantling why and how these specific elements interact and contribute to the overall effectiveness in order to tackle possible threats to the construct and external validity of the specialised treatment. With respect to the construct validity; although the sound-based approaches might offer a sense of control to patients, which would be beneficial for treatment outcomes, they might also provide a means of escape or avoidance of the tinnitus perception (McKenna & Irwin, 2008), possibly contributing to tinnitus-related fear in the long run. Sound-based therapy might therefore also be counterproductive in the habituation processes. Presently, the benefit of treatment elements based on TRT, the sound-based approaches (such as the prescription of masking devices and hearing aids to benefit tinnitus), and those aimed at the sound perception levels (sound-enrichment aimed at the alteration of the acoustical perception of the tinnitus) are most ambiguous in how they influence the overall effectiveness of the present treatment. Also, it has been suggested that TRT as an additional treatment approach to CBT has no additional beneficial effects (Hiller & Haerkötter, 2005), and the evidence for TRT and other sound-based approaches as well as treatment directed towards the alteration of the tinnitus signal is poor (Hoare, et al., 2011; Hoare, et al., 2010; Phillips & McFerran, 2010). Additionally, though these sound-based treatment elements did differ between the treatment arms, they might have differed only slightly and the effects might have been cancelled out in the comparative analyses. One of the reasons of the weak effects of sound-based treatments might be that inter-individual differences in what exactly the CS is may have been omitted. In standard exposure treatments, idiosyncratic fear stimuli are identified and a fear hierarchy is established before patients are (gradually) exposed to the CS without the option to avoid them.

External validity and implementation challenges

The present RCT was the first to investigate the effectiveness of this integrative approach. The treatment centre might have represented a unique setting, with unique resources, and a unique patient group. A possible threat to the external validity is the unique setting in which it was conducted. It is recommendable to replicate the study in a different clinical setting. Another important issue concerning the external validity is the unique combination of individual treatment elements, and interactions between them might have influenced the effects without our knowledge. To tackle these possible threats to the external validity the implementation and evaluation of the current treatment across different patient groups is needed, as well as a dismantling approach and investigations of different combinations of treatment elements. Also, an unanswered question is whether the results generalise to later time points. Long-term effects of our approach are still undiscovered. The effects of the CBT-based treatment have been established over a period of 12 months, with a no-treatment follow up of only 4 months. Whether these effects are sustained in the long run is still unclear. Future studies should incorporate measurements of effects over longer periods of time. This holds as well for economic evaluations. As we have discovered, CBT based tinnitus treatment is more cost-effective as care as usual, though results pertain to a period of 12 months only. Whether these cost-effect benefits hold over longer periods of time is still to be established as well.

The need for objective measures

Noteworthy about present findings is that they all are based on measurements of constructs operationalised using only one single method, namely: self reports. This poses a threat to the construct validity of present findings. Relying on the patients self-report only may compromise the validity of the findings as they may be subject to various self-protecting biases. It would be interesting to investigate whether the psychological mechanisms, i.e. constructs under investigation, are associated with more objective measures such as ‘maskability’ of the tinnitus, sound tolerance levels, physiological measures or observable behavioural changes. For example, we might consider the reflexive responses pertaining to the audiological system, such as the *stapedius reflex* and the *tensor tympani contraction*. It is as of yet unclear whether these are purely auditory reflexes, whether they can be voluntarily evoked, or behave similarly to a *startle reflex* (Bhimrao, Masterson, & Baguley, 2012).We know these reflexes are automatically evoked by moderate to loud sounds; it might be interesting to investigate whether these reflexes can be modulated by psychological variables, such as heightened fear or threat value of sounds.

Clinical versus statistical significance

A further important observation is that despite the new developments and results we have reported at present, and despite the positive reports on the benefits of the CBT-based treatment in increasing general quality of life, as well as decreasing tinnitus severity and impairment on a global level, there still remains a fairly large group of patients who, even after intensive treatment, have a remaining bothersome and still tinnitus and suffer on a daily basis (Hesser, et al., 2012). The role of tinnitus-related fear has been suggested to be of key importance, however the need to fine-tune our current CBT interventions, by dismantling and investigating the processes of change underlying the effects, or the absence of effects, as a result of CBT treatment, is pressing, since these mechanisms are still largely unknown and likely to differ across patient groups having other clinical demands.

An urgent need exists to accumulate higher levels of evidence for existing tinnitus treatment approaches. The severe limitations of past research have led to suggestions for a methodological standard for future research endeavours in the clinical tinnitus-research field (Landgrebe, et al., 2012). It was recommended that first, in planning the trial, a clear research question has to be formulated, and the trial-design needs to be adequately adapted to a clearly formulated research question, to be answered with the use of clearly defined main outcome measures. Registration in a clinical trials registry, ethical approval and informed consent are imperative. Sample size estimations have to be based on power calculations, and a description of a statistical analysis plan needs to be present. When performing the clinical trial as well as in the reporting of results good clinical practice (GCP) and CONSORT guidelines should be followed and we should aim at publishing all clinical trials, even when results are not statistically significant.

Additionally, we have to consider the meaningfulness of the results obtained by the methodology applied at present. While we have discovered evidence of statistically significant differences between groups of patients, and have evaluated the size of these effects over time, indicating the effectiveness of the CBT based treatment, we still need to uncover the meaning of these results, or the practical importance thereof for the individual patient within these groups. It is warranted to investigate whether the improvements are reliable, in other words, are there different levels of improvement across patients within a group, how large was the proportion of patients who did not improve, in whom are they large enough to be meaningful, and moreover, are these improvements noticeable by the individual patient themselves, their social environment, or the professionals involved. (Lambert & Ogles, 2009; Ogles, Lunnen, & Bonesteel, 2001)

What for whom? Customizing tinnitus treatment

And finally, at present the theoretical frameworks provided by the NP model and the CB model have guided the largest part of the research. However, as has been stated before, there are some questions that still remain unanswered. The question as to why tinnitus becomes a chronic disabling condition in a small part of individuals only, might be a very relevant one and should be addressed in future research. Further elaboration of the current theoretical frameworks is needed to answer this question, and could lie in the direction of the following concepts; the context in which the tinnitus arises, personal traits or characteristics of the individual and even demands placed on the individual at the time when the sound becomes bothersome or not.

We can conclude that tinnitus treatments in general, whether CBT-based or other, are diverse, usually consist of multiple elements, evidence based treatment options are scarce, a standard approach in the treatment for tinnitus is missing, as are standard diagnostic heuristics, and intervention studies and clinical trials in the past have to many critical methodological limitations to infer sound conclusions for clinical practice as of yet (Landgrebe, et al., 2012). As a result, usual tinnitus health care practice remains fragmented, mainly aimed only at the masking of the tinnitus perception, and is diverse within countries, settings and within the disciplines involved, frustrating not only clinicians but more importantly leaves many patients empty-handed (Cima, et al., 2009; Hoare, et al., 2012). Elaborations on current theoretical frameworks, and an integrative approach, not only in research endeavours and treatment development, but also in choosing outcomes and diagnostic assessment, might lead us faster towards high quality research, standards for tinnitus assessment, and eventually effective tinnitus treatments, increasing evidence-based intervention options for larger groups of patients.

The merits of well designed large-sampled RCT's and inferential statistical analyses in current evidence-based research are often advocated, however, some issues are worth considering. What do the group-based conclusions resulting from an RCT tell us about the individual patient in the sample; more importantly, what to do with patients in which the group-generalizations do not hold? How can we detect what works for whom, how can we make discriminations about kinds of patients, types of treatment elements, and even relevant outcomes? We need to consider additional methods of investigation to help us disentangle the generalized conclusions in order shed light into these issues. Purposive sampling methods or single case studies might be essential to discover the more sensitive changes in the individual patient, the relevant measures to detect them, in order to develop and target our treatments elements more precisely and combine them more effectively. (Shadish, Cook, & Campbell, 2002; Vlaeyen & Morley, 2005)

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SUMMARY

Summary

Tinnitus Aurium, or the ringing of the ear(s), is a fairly common auditory perception, experienced at least once in life by almost everybody. The term 'tinnitus' is still fairly unknown by the general public however, and, more importantly, the observation that some individuals suffer severely on a daily basis, is even less known. Tinnitus is furthermore not traceable to disease, injury, or pathology in the brain or elsewhere, presenting us with difficulties in assessing and treating the suffering patient. The aim of the present thesis is to introduce new cognitive behavioural concepts in tinnitus assessment, treatment, and research approaches, to shed light into current state of evidence, into current tinnitus health care in The Netherlands, and to provide directions for a standard care approach in assessment and treatment

In *Chapter 2* a systematic review reveals that current treatment approaches in tinnitus management are highly diverse; consist of combinations of different treatment elements, and tinnitus diagnostics and outcome assessments differ widely, not only across investigations, but as well across treatment approaches, and clinical settings. The lack of a standard diagnostic algorithm and therefore heterogeneous outcomes of the included studies leads to challenges in interpretability and comparability. An overall CBT based approach is recommended, since evidence for this approach seems most promising. Additionally, the evidence for the benefits of sound-therapy is considered to be modest at best.

In *Chapter 3* a novel measure for tinnitus related interference in daily functioning is presented. Other viable tinnitus assessment measures, of high psychometric properties already exist. Even though these are of high value in clinical practice, most are hybrid, including items referring to concepts other than disability, such as distress, cognitive impairments, emotional problems, and attentional deficits. When investigating underlying mechanisms in tinnitus suffering, or when comparing tinnitus outcomes to other health problems, the need for a conceptually sound measure of daily life functioning arises. The Tinnitus disability index (TDI) is evaluated on psychometric quality, and results indicate it is a valid and reliable brief and easily administered index, capturing tinnitus disability, a unique construct.

In *Chapter 4*, three novel measures assessing catastrophising about tinnitus, fear of tinnitus, and increased awareness of the tinnitus are introduced. In a cross-sectional investigation with 615 participants, tinnitus-catastrophizing is associated with tinnitus-related fear and increased tinnitus-awareness. Higher levels of tinnitus-related fear in turn are associated with increased awareness towards the tinnitus. Finally, catastrophic misinterpretations of tinnitus are significantly related to poorer quality of life ratings. In a subsequent mediation analyses it is revealed that tinnitus-related fear fully mediates the association between tinnitus catastrophizing and quality of life.

In *Chapter 5*, a research protocol is proposed for a randomized controlled trial, investigating the effectiveness and cost-effectiveness of a novel stepped care multidisciplinary tinnitus treatment approach as compared to care as usual. A standard approach in tinnitus health care, a common diagnostic heuristic, or effective treatment strategy is lacking. Cognitive behavioural therapy (CBT) is the most evidence-based method for effectively relieving tinnitus complaints. Best-practice evidence indicates that audiological treatment for tinnitus is mostly based on TRT, since this approach offers standard guidelines in audiological counseling and education. First, a novel CBT-based tinnitus treatment protocol, which includes the TRT counseling principles, is described. Second, a large scale randomized controlled trial is proposed, to study the effectiveness and cost-effectiveness of this specialised CBT-based tinnitus treatment protocol, as compared to care as usual. Care as usual is the treatment as provided by a typical audiological centre in the Netherlands, and consists of mainly audiological diagnostics and rehabilitation aimed at the sound-perception level by ear-level devices (hearing aids and sound-generators). Both treatment arms within the trial are organized in a stepped care manner, in which intensity of care increases in two consecutive steps, serving the largest part of the patient population with treatment in a fairly short first step, and providing an additional step 2 for those suffering on a more severe level.

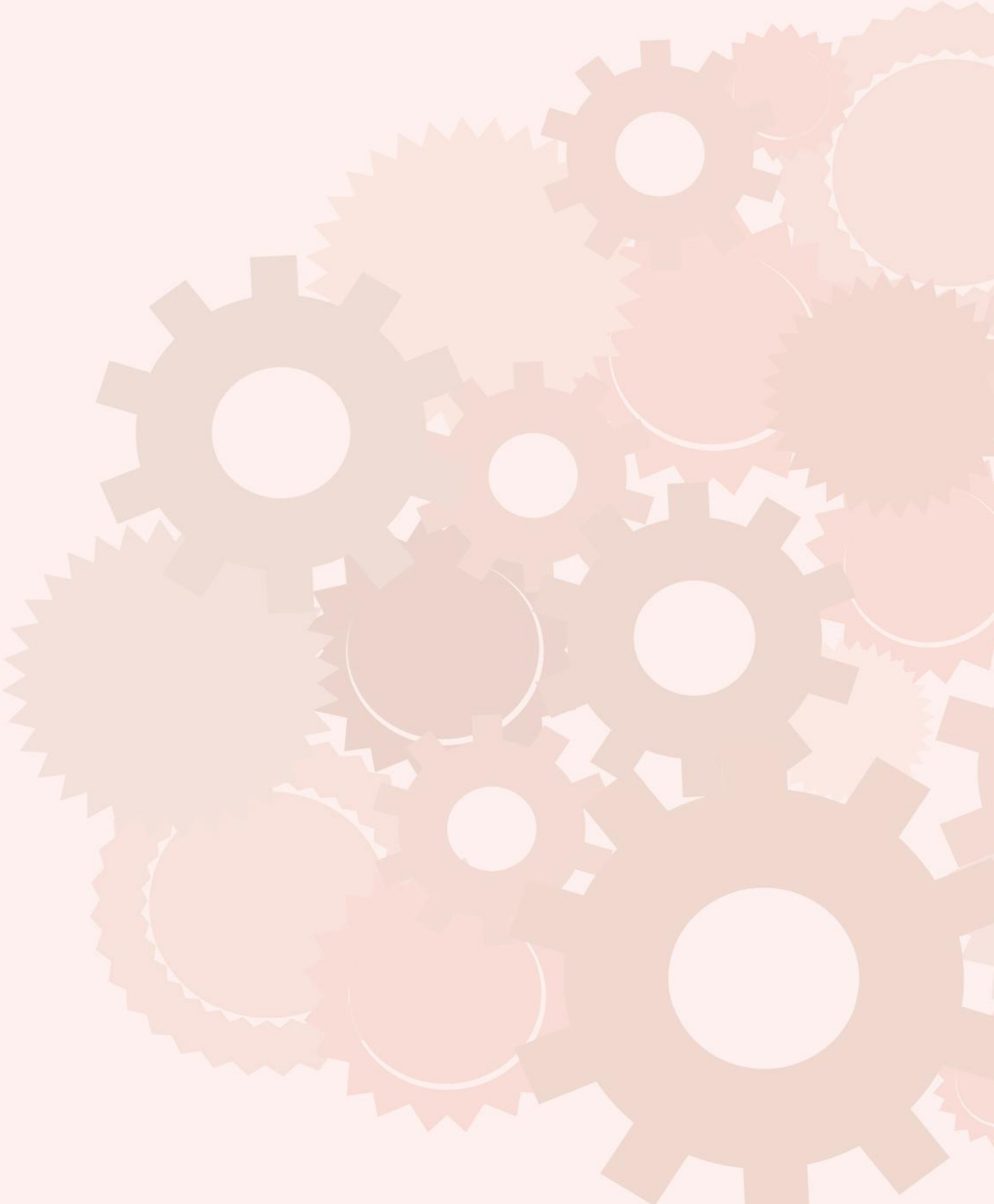
In *Chapter 6*, results from the RCT, investigating the effectiveness of this new specialised CBT-based tinnitus-treatment protocol are presented. Results demonstrate that specialised CBT-based tinnitus treatment (specialised care = SC), organized in two consecutive steps, combining the counselling elements of TRT within an overall CBT-framework, is more effective than the care that is usually provided throughout the Netherlands (usual care = UC), consisting of audiological diagnostics and rehabilitation aimed at the sound-perception level. Findings support that SC is more effective in increasing health-related quality of life, and reducing tinnitus-severity and tinnitus impairment. Additionally, SC compared to UC generates greater improvements in general negative emotional states, and results in decreased levels of tinnitus-related catastrophic thinking and tinnitus-related fear.

In *Chapter 7*, a subsequent extensive economic evaluation, comparing care as usual with the specialised CBT-based treatment, is described. Tinnitus related health care costs; both for care consumed at the treatment centre as well as care provided in other medical settings, patient and family costs, and costs for loss of productivity are included in the analyses, offering both the societal and the health care perspective. The incremental cost effectiveness ratio (ICER), calculated using the primary effect parameter Quality Adjusted Life Year (QALY), indicates that the stepped-care CBT-based approach, compared to care as usual, is cost-effective.

In *Chapter 8*, the mediating role of tinnitus-related fear is investigated; it is hypothesized that tinnitus related fear explains the beneficial effect of the stepped-care CBT approach, compared to care as usual. Post hoc analyses on the outcomes of the RCT reveal that patients in the specialised treatment group are significantly less impaired by their tinnitus, partly as a result of decreased tinnitus-related fear. That is, decreases in tinnitus related fear partly explain why participants in the SC treatment, when compared to those in the UC treatment, experience higher health related quality of life, less severe complaints, and less tinnitus related impairment. Results also indicate that the mediating effect of tinnitus-related fear on tinnitus related impairment specifically, is moderated by patient's participation in step 2 SC treatment. That is, in the SC treatment, especially for patients who were treated in an additional second step, decreases in tinnitus related fear explain why they are less impaired by their tinnitus in daily life.

In *Chapter 9*, a general discussion of the present findings is provided. First, the main theoretical frameworks of the present thesis are presented, and strengths and weaknesses are discussed. Second, the main findings are summarized and subsequently an integrated discussion of all findings is provided. Last, the implications of the present findings for theory and practice, the limitations of the present results, and directions for future research are discussed. Present findings support the importance of applying a cognitive behavioural framework and addressing tinnitus-related fear and fear-responses in the treatment of patients with chronic disabling tinnitus.

SAMENVATTING



Samenvatting

Tinnitus aurium betekent letterlijk ‘het rinkelen van de oren’ en wordt in de volksmond ook wel oorsuizen genoemd. Het is een veel voorkomend auditief fenomeen; bijna iedereen kan wel eens een tinnitus kan waarnemen. De term ‘tinnitus’ en het feit dat sommige mensen hierdoor ernstig belemmerd worden, is echter nog redelijk onbekend. Chronische tinnitus kan niet worden herleidt tot een ziekte, lichamelijk letstel, of pathologie van het brein en is om deze reden vaak een moeilijk meetbaar en bijna onbehandelbaar probleem. Het huidige proefschrift introduceert nieuwe cognitieve en gedragsmatige concepten voor de diagnostiek en behandeling van de tinnitus klacht. Deze nieuwe concepten kunnen worden toegepast in toekomstig onderzoek, in de ontwikkeling van effectievere behandelmethoden, en ook betrouwbare diagnostiek; zij kunnen bijgedragen aan een toekomstige standaard voor tinnitus diagnostiek en behandeling.

In *Hoofdstuk 2* wordt een systematisch literatuuronderzoek beschreven. De meeste tinnitus behandelingen die tot op heden zijn onderzocht, blijken moeilijk met elkaar te vergelijken. Er bestaan grote verschillen in de diagnostiek en behandelelementen die worden toegepast, en in het meten van resultaten uit onderzoek. Het gebrek aan standaard diagnostiek en de grote verscheidenheid aan uitkomstmaten leidt tot moeilijkheden in het interpreteren en vergelijken van de resultaten uit eerder onderzoek. Niettemin is de meeste evidentie gevonden voor een cognitief gedragsmatige aanpak. De evidentie voor geluidstherapie is vooralsnog als matig te beschouwen.

In *Hoofdstuk 3* wordt een nieuw meetinstrument geïntroduceerd. Deze meet in hoeverre tinnitus een invloed heeft op activiteiten van het dagelijks leven. Er zijn in het verleden al geschikte en valide meetinstrumenten van hoge psychometrische kwaliteit ontwikkeld. Hoewel deze waardevol zijn gebleken in de klinische praktijk, zijn de meeste hybride. Dat wil zeggen dat de meeste al bestaande instrumenten, naast algemene tinnitus belemmering, verschillende concepten simultaan meten, zoals psychologische zorgen, cognitieve belemmering, emotionele problemen en problemen in aandachtsprocessen. Als we onderliggend mechanismen willen bestuderen, of als we de tinnitus klachten willen vergelijken met andere gezondheidsgerelateerde problemen, dan hebben we een instrument nodig welke het functioneren in het dagelijks leven meet, zonder deze andere constructen te betrekken. De ‘Tinnitus Disability Index’, is mogelijk een goede kandidaat en wordt op psychometrische kwaliteiten getoetst. Het lijkt erop dat de ‘Tinnitus Disability Index’ inderdaad een valide en betrouwbare maat is. Het instrument is kort, makkelijke af te nemen, en meet een uniek onderliggen concept, namelijk, de invloed van tinnitus op dagelijkse activiteiten.

In *Hoofdstuk 4,* worden 3 nieuwe meetinstrumenten geïntroduceerd, te weten; Catastroferen over tinnitus, verhoogde aandacht voor de tinnitus en tinnitus gerelateerde vrees. Uit een cross-sectioneel onderzoek met 615 deelnemers blijkt dat catastroferen over tinnitus is geassocieerd met zowel tinnitus gerelateerde vrees als verhoogde aandacht voor de tinnitus. Hogere vrees voor de tinnitus is vervolgens geassocieerd met verhoogde aandacht voor de tinnitus, en catastroferen over tinnitus met lager kwaliteit van leven scores. In een mediatie analyse bleek dat deze laatste associatie, volledig werd gemedieerd door tinnitus gerelateerde vrees.

In *Hoofdstuk 5* wordt een onderzoeksvoorstel gepresenteerd. De effectiviteit en kosteneffectiviteit van een nieuwe multidisciplinaire tinnitus behandeling, trapsgewijs georganiseerd, zal worden vergeleken met de gebruikelijke tinnitus zorg zoals deze in Nederland plaatsvindt. De standaard aanpak op gebied van tinnitus zorg, een gemeenschappelijk kader voor diagnostiek, of een effectieve behandelstrategie, zijn nog niet voorhanden. De cognitieve gedragstherapie (CGT) is tot op heden het meest effectief gebleken in het verminderen van de tinnitus klachten. De audiologische behandelwijze wordt veelal gebaseerd op de Tinnitus Retraining Therapie (TRT), omdat deze aanpak een gestandaardiseerde manier voor het leveren van audiologische zorg biedt. In het huidige onderzoeksprotocol worden de CGT en TRT methoden gecombineerd. Er wordt een grootschalige gerandomiseerde gecontroleerde trial (RCT) voorgesteld om dit gespecialiseerde CGT behandelprotocol te onderzoeken, en te vergelijken met de gebruikelijke zorg. In Nederland bestaat de gebruikelijke zorg voornamelijk uit audiologische diagnostiek en consultatie, bestaande uit het voorschrijven van hoortoestellen, geluidsgenererende toestellen en het bieden van geruststelling en uitleg over de tinnitus. In geval van ernstige tinnitus klachten wordt de patiënt doorverwezen naar maatschappelijk werk. In de RCT zullen beide condities zullen worden georganiseerd op een trapsgewijze manier, met een redelijke korte interventie periode in de eerste trap, en een intensiever behandeling in een tweede aanvullende trap, voor hen die aan een meer ernstige vorm van tinnitus lijden.

In *Hoofdstuk 6* worden de resultaten uit de RCT beschreven. De gespecialiseerde trapsgewijze CGT behandeling, waarin de TRT consulten worden gecombineerd en toegepast binnen een CGT-kader, is effectiever gebleken dan de gebruikelijke zorg, welke voornamelijk bestaat uit audiologische consultatie gericht op de geluidsperceptie. De gespecialiseerde trapsgewijze CGT behandeling is effectiever dan de gebruikelijke zorg in het verhogen van de kwaliteit van leven van tinnitus-patiënten, in het verlagen van de psychologische problemen ten gevolge van de tinnitus en in het verbeteren van de algemene tinnitus belemmering. Ook was de CGT behandeling effectiever in het verlagen van vrees en cognitieve problemen ten gevolge van de tinnitus, alsook algemene gevoelens van angst en depressie.

In *Hoofdstuk 7* wordt een economische evaluatie van de gespecialiseerde CGT behandeling ten opzichte van de gebruikelijke zorg beschreven. Tinnitus gerelateerde gezondheidszorg kosten, de kosten die zijn gemaakt in het behandel centrum, de gemaakte kosten in andere medische instellingen, patiënt en familie kosten, kosten ten gevolge van werkverzuim en verlies aan productiviteit, worden meegenomen in de analyse. De economische evaluatie kan hierdoor worden uitgevoerd vanuit zowel het maatschappelijk als het gezondheidszorg perspectief. De incrementele kosteneffectiviteit ratio (ICER), met als primaire effect parameter een 'Quality Adjusted Life Year' (QALY), toont dat de trapsgewijze CGT behandeling, als we deze vergelijken met de gebruikelijke tinnitus zorg, kosteneffectief is.

In Hoofdstuk 8 wordt de rol van tinnitus gerelateerde vrees verder onderzocht. Er wordt gesteld dat tinnitus gerelateerde vrees verklaart waarom de trapsgewijze CGT behandeling effectiever is dan de gebruikelijke tinnitus zorg. Post hoc analysen op de uitkomsten van de RCT tonen dat patiënten in de CGT behandeling significant minder belemmerd zijn door hun tinnitus ten gevolge van een daling in de vrees voor tinnitus. Dat wil zeggen dat een vermindering in tinnitus gerelateerde vrees verklaart waarom patiënten in de CGT behandeling, vergeleken met de gebruikelijke zorg, een betere kwaliteit van leven tonen, minder ernstige klachten rapporteren, en zich minder belemmert voelen door de tinnitus. De resultaten wijzen ook op het feit dat dit sterker het geval is voor de patiënten die in de aanvullende tweede trap zijn behandeld.

In Hoofdstuk 9 wordt een algemene discussie over alle bevindingen gepresenteerd. Eerst worden de theoretische kaders van het huidige proefschrift toegelicht en worden zwakke en sterke punten van de theorieën beschreven. Vervolgens worden de belangrijkste bevindingen samengevat, waarop een geïntegreerde discussie volgt. Ten laatste worden de implicaties voor de klinische praktijk en de limitaties van de huidige bevindingen beschreven, en worden er aanbevelingen gedaan voor verder onderzoek. De huidige bevindingen ondersteunen het belang van een cognitief gedragsmatig raamwerk, en de belangrijke rol van tinnitus gerelateerde vrees en vreesreacties, in de behandeling van patiënten met een chronisch belemmerende tinnitus.

DANKWOORD

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CURRICULUM

About the author

Rilana Filomena Franca Cima was born in Heerlen (The Netherlands) on January 5, 1976. In 1995 she graduated from secondary school Rombout's College, in Brunssum (The Netherlands). In September 1995 she started International Business at Maastricht University and received the propedeusis in 1996. This is when she started studying Psychology at Maastricht University and received her master's degree in psychology by the end of 2000. At that time she started the two-year master program User- system Interaction at the Technical University of Eindhoven, and received her master's of technological design in 2002. She started working as a researcher in usability-design at the iRv, Institute for Rehabilitation. In 2004 she changed paths and started as a clinical psychologist at Adelante, audiology and communication. By the end of 2005 opportunity arose to start working on a research proposal for the Netherlands Organisation for Health Research and Development (ZonMW), for the current PhD project. The research proposal was awarded a grant by the end of 2006, and in January 2008 she started a part-time PhD-trajectory at the department of clinical psychological science at Maastricht University. Part of the research for this PhD project was carried out in corroboration with Adelante, audiology and communication, the department of audiology of the Maastricht university hospital (AzM), and the research groups Health Psychology and Experimental Oto-Rhino-Lanryngology (ExpORL) at the KU Leuven. Since October 2012 she has a research position at Adelante, centre of expertise in rehabilitation and audiology, and is responsible for the audiology research-line. She continues her research at the department of clinical psychological science at Maastricht University, and her clinical work at Adelante, audiology and communication.

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