Hearing Research xxx (2013) 1–9

Contents lists available at SciVerse ScienceDirect

Hearing Research

journal homepage: www.elsevier.com/locate/heares

Research paper

Standardized tinnitus-specific individual cognitive-behavioral therapy: A controlled outcome study with 286 tinnitus patients

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ARTICLE INFO

Article history:
Received 13 July 2011
Received in revised form
13 October 2012
Accepted 12 November 2012
Available online xxx

ABSTRACT

Background: Pharmacological treatment of tinnitus cannot be considered well established. Thus, reducing tinnitus severity through behavioral therapy is emerging as a key goal.
Methods: A total of 286 patients suffering from persistent and stable tinnitus for four months or longer participated in this controlled clinical multicenter study. The study investigated the efficacy and safety of a standardized treatment involving individual cognitive-behavioral therapy (CBT). Controls were 120 patients waiting to be treated. Therapy was standardized using manualized procedures within the setting of a specifically designed disease management program. The primary outcome measure was the tinnitus change score using an 8-point numeric verbal rating scale. Secondary outcome measures were tinnitus severity as determined by the tinnitus questionnaire score as well as the tinnitus loudness score and the tinnitus annoyance score using 6- and 8-point numeric verbal rating scales, respectively. Following a significant multivariate rank test, these four validated outcome measures were tested in the order given.
Results: The primary outcome measure, tinnitus change score, showed an efficacy of treatment with an odds ratio of 3.4 (95% confidence interval, 2.6–4.5). Of the treated patients, 84% showed a tinnitus change score improvement, but only 22% of controls did. The secondary outcome measures of tinnitus questionnaire score, loudness score, and annoyance score improved in the treatment group significantly more than in the control group. In the therapy group, the tinnitus questionnaire score was reduced by 50% from a median of 27 to 13.5; in the control group, no change in median tinnitus questionnaire score was observed. The multivariate endpoint of the primary and secondary outcome measures differed significantly ($P < 0.0001$) between treatment and control groups. The same was true when univariate scores were considered.
Conclusions: A structured tinnitus-specific CBT using standardized tinnitus-specific interventions can be an effective individual therapy for the treatment of patients suffering from tinnitus for at least 4 months. The trial was registered at the ClinicalTrials.gov registry (ID: NCT 00719940).

1. Introduction

1.1. Background

Chronic tinnitus affects between 5 and 15% of the adult population in industrialized nations (Heller, 2003). A significant impairment of quality of life resulting from tinnitus is observed in 1–3% of the population (Axelsson and Ringdahl, 1989; Dobie, 2003). Quantification of the burden of disease by the World Health

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0378-5955/$ – see front matter © 2012 Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.heares.2012.11.013

Organization shows that the global burden of disabling tinnitus in Western countries is higher than the burden of disease of various other well-recognized health problems (Deshaies et al., 2011).

Pathogenetic tinnitus may be symptomatic, but in the majority of cases, the disorder remains idiopathic (Møller, 2003; Preyer and Bootz, 1995). Pathophysiologically, primary damage in the cochlea is usually assumed (peripheral tinnitus; Georgiewa et al., 2006; Mazurek et al., 2006; Møller, 2003; Preyer and Bootz, 1995; Tonndorf, 1977). Regardless of whether tinnitus has an idiopathic or symptomatic peripheral origin, a secondary centralization of tinnitus has been suggested to be the dominant contributor to the burden of disease of many patients with subacute and chronic tinnitus (Hallam et al., 2004; Jastreboff, 1990; Jastreboff and Hazell, 1993; Tyler, 1981; Zenner, 1998; Zenner et al., 2006). The origin of tinnitus from lesion-induced plasticity of the auditory pathways and the brain network involving limbic and other nonauditory regions has recently been reviewed (Rauschecker et al., 2010; Roberts et al., 2010). Supplementary neurophysiological models have been advanced to explain tinnitus centralization (Tyler, 1981), including (i) the development of a conditioned response (Jastreboff, 1990) and (ii) the lowering of the cognitive threshold (cognitive sensitization; Zenner et al., 2006). The conditioned response model has been challenged by Noble and Tyler (2007). Tinnitus sensitization corresponds to earlier described tinnitus effects on cognitive efficiency (Hallam et al., 2004). Thus, many patients may suffer from a combined peripheral and central disorder involving emotional and cognitive determinants. In addition, psychosocial factors may contribute to a decompensated complex tinnitus (Georgiewa et al., 2006; Mazurek et al., 2006).

Pharmacological treatment effects on both cochlear damage and centralized tinnitus cannot be considered well established (Dobie, 1999). For the treatment of a conditioned reflex at the subcognitive level, a retraining therapy (Jastreboff, 1999, 2007a) has been suggested, i.e., a combination of extinction-inducing acoustic therapy applying 'noise generators' (Jastreboff, 2007b) and a 'directive counseling' to reduce negative emotions (Jastreboff, 1999, 2007a; Zachriat and Kröner-Herwig, 2004). For interventions at the cognitive level, cognitive-behavioral therapy (CBT) may be applied (Martinez-Devesa et al., 2010). Classical CBT is characterized by a high therapeutic freedom and variability with iterative adaptation of the procedures (Fritsche and Kröner-Herwig, 1997). As such, the therapeutic processes for different patients are not explicitly standardized and are difficult to compare or reproduce. Structured CBT reduces the problem of comparability and reproducibility by applying standardized interventions. Results from controlled studies of structured and standardized CBT, however, are available only for a group setting (Kröner-Herwig et al., 1995, 2003). Patients often reject group treatment, though, asking instead for an individual setting for addressing their personal problems with tinnitus.

1.2. Rationale

In the current work, tinnitus-specific interventions originally designed for group interventions (Delb et al., 2002a,b; Fritsche et al., 1997) were modified and applied as an individual therapy. To test the effectiveness of a standardized individual CBT, both the tinnitus-specific interventions and therapeutic course were standardized, and all procedures were available in a treatment manual. To standardize and structure decision making, the interventions were integrated within an earlier developed specific disease management program (DMP), designated as the structured tinnitus care program (Zenner and Zalaman, 2005). Two preliminary studies (Zenner and de Maddalena, 2005) describing the first results of these modified interventional procedures as individual therapies with 273 patients suggested that the group-specific features of interventional procedures may not be critical for outcome.

1.3. Objectives

The purpose of the present study was to test the hypothesis that a standardized tinnitus-specific CBT in the individual clinical setting is efficacious when compared with non-treatment.

2. Methods

2.1. Trial design

This multicenter (5 sites), parallel waiting group-controlled study with an allocation ratio of 1.3:1 and addressing the efficacy and safety of standardized tinnitus-specific interventions within an individual CBT was set in one Tübingen hospital unit and four outpatient clinics at referral centers in Aschaffenburg, Frankfurt, and Tübingen, Germany. Standardized interventions were predefined within the structured tinnitus care DMP. Safety reporting followed the good clinical practices standard.

2.2. Participants

2.2.1. Condition

The condition was a non-acute, persistent and stable tinnitus aurium that patients had experienced for longer than 11 weeks. Table 1 describes the demographic and baseline data with details regarding sex and age distribution, tinnitus lateralization, tinnitus duration, the acoustic quality of the tinnitus, the Goebel–Hiller score (TQS, tinnitus questionnaire score), the tinnitus loudness score (TLS), and the tinnitus annoyance score (TAS). On the basis of the TQS, the loudness score, and the annoyance score, the severity of the tinnitus at baseline was equal in both treatment and control groups (Table 1).

2.2.2. Inclusion and exclusion criteria

Participating patients had to fulfill the following inclusion criteria: persistent and stable tinnitus for >11 weeks, normal findings using an ear microscope, normal tympanic membrane mobility and stapedial reflex, ability to fill out relevant questionnaires, and gap

Table 1
Patients and symptoms at baseline.

Patients	Experimental group	Control group	OR (CI)
Sex, m : f	112 : 54	76 : 44	1.2 (0.73–2.0)
Age, mean (s), difference	48.5 (14)	46.3 (15)	2.2 (−1.8–6.2)
Tinnitus			
Left : middle or both : right	37 : 91 : 37	38 : 52 : 30	0.91 (0.73–1.1)
Duration			
4 to 12:	50% (83/165)[a]	12% (14/120)	7.7 (4.1–14)
>12 months	50% (82/165)	88% (106/120)	
Quality			$\chi^2 = 13.6$
Whistling	78 (47%)	16 (46%)	($P = 0.0036$)
Buzzing	6 (4%)	4 (11%)	
Narrow band noise	28 (17%)	12 (34%)	
Other	53 (32%)	3 (9%)	
Tinnitus compensation			
Compensation : decompensation	95 : 71	93 : 27	2.6 (1.5–4.4)
Tinnitus questionnaire score			
Median (quartiles)	27 (18–2.5)	28.5 (15–46.5)	1.04 (0.84–1.27)
Loudness score			
Median (quartiles)	3 (2–4)	3 (2–4)	0.91 (0.73–1.12)
Annoyance score			
Median (quartiles)	4 (3–5)	4 (2.5–5)	0.88 (0.71–1.08)

OR = odds ratio, i.e., the parameter tested for equality with 1 by Fisher's exact test for dichotomous features and by ordinal logistic regression for ordinal variables; CI = 95% confidence interval.

[a] Missing data from a patient.

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between the sound pressure level in the audiometric tinnitus matching (tinnitus level above threshold) and the tinnitus loudness using the TLS (Zenner and de Maddalena, 2005). Exclusion criteria included: pulsatile, intermittent, or non-persistent tinnitus, tinnitus as a concomitant symptom of a known systemic disease (such as vestibular schwannoma, endolymphatic hydrops, or Menière's disease), known retrocochlear hearing defect (such as those detected through brainstem evoked response audiometry), conductive hearing loss exceeding 10 dB at two or more frequencies, ear canal or middle ear inflammation or effusion, one or two sided total deafness, status following a craniocerebral trauma, cervicogenic or stomatognatogenic tinnitus, start of therapy with maskers ≤2 months preceding therapy, start of autogenic training or psychotherapy <4 weeks before therapy, ongoing acupuncture therapy, drug treatment for tinnitus within 24 h preceding therapy, other concomitant tinnitus treatment, inability to discontinue drugs known to be associated with tinnitus (high-dose aspirin, quinidine, aminoglycosides) or psychotropic medication prior to entry into the study, epilepsy, Parkinson's disease or dementia, acute allergic disease, neurological or psychiatric disease or drug or alcohol abuse that would interfere with regular completion of the study, consuming diseases, history of a severe ischemic disorder (previous stroke, previous heart attack, peripheral arterial occlusion disease), exposure to an investigational agent within the previous 4 weeks, anticipated non-availability for study visits or procedures, or insufficient command of German.

2.2.3. Examinations

To check for inclusion and exclusion criteria, patients underwent a detailed otological and audiological workup including case history, ear microscopy, pure tone audiometry, tympanometry, stapedial reflex measurement, and transiently evoked otoacoustic emissions (TEOAEs), as well as audiometric tinnitus matching by frequency and by sound pressure level (above hearing level). History and examination results were recorded in a case record form (CRF) predefined before enrollment of the first study patient. Data recorded were inclusion and exclusion criteria, tinnitus duration, tinnitus noise quality, tinnitus lateralization, preceding and accompanying diseases, and preceding treatments including the intake of drugs (Table 2). To enable a standardized procedural selection algorithm for the therapist (Fig. 1), a standardized biographic interview with a subsequent structured evaluation was carried out according to the guidelines of the structured tinnitus care DMP. The structured interview covered the following 11 parameters, each subdivided into 2–10 subparameters: loss of control, subjective suffering at different levels, subjective disease model, negative counseling, coping strategies, limitations on rational thinking, auditory perception and communication, hyperacusis, impairments of coping resources, tinnitus-induced comorbidities, and a disease-maintaining function of the tinnitus. Furthermore, patients were examined using three validated (Goebel and Hiller, 1994; Zenner and de Maddalena, 2005), self-administered scales. The TQS was included along with its subscores (Goebel and Hiller, 1994); this tinnitus questionnaire is a validated 52-item self-rating scale for emotional (E) and cognitive (C) distress, intrusiveness (I), auditory perceptional difficulties (A), sleep disturbances (SL), and somatic complaints (SO). It is the German version derived from the English TQS of Hallam et al. (1988). The TLS was determined using a validated 6-point rating scale and the TAS evaluated using a validated 8-point rating scale (Table 3; Zenner and de Maddalena, 2005). At the end of therapy, tinnitus change was recorded as a tinnitus change score using a validated 8-point numeric verbal rating scale (Table 3; Zenner and de Maddalena, 2005). All scores had been validated in earlier studies (Goebel and Hiller, 1994; Zenner and de Maddalena, 2005). Adverse events were recorded in the CRF.

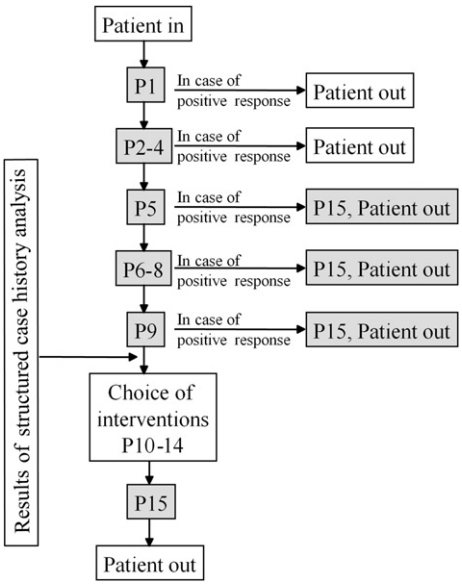

Fig. 1. Procedural course and procedural selection algorithm for the therapist. P1–P15 indicate the procedures used in the respective session from Table 4. Gray boxes represent a session of approx. 50–60 min (except P1: 1 or 2 sessions). The procedures were applied up to P9 in the indicated sequence. If a clear improvement in symptoms was recognizable according to the tinnitus change score after one of the first 9 procedures ("positive response"), the therapy was finished as indicated either without or with procedure P15 (arrows to the right). If a positive response was not achieved, the therapy was continued in the direction of the downward arrow. "Choice of interventions" means that an additional 1–5 sessions of approx. 50–60 min each, P10–P14, were selected on the basis of the results of the structured case history analysis when no positive response was detected upon completion of P9.

Table 2
Pretreatment of 92/286 patients prior to inclusion into the study.[a]

Pretreatment	% (n)
No pretreatment	68 (194)
Vasoactive drugs	18 (51)
Cervical spine therapy	6 (17)
Phytotherapy	4 (11)
Acupuncture	3 (10)
Behavioral therapy	2 (7)
Relaxation exercises	2 (5)
Counseling	1 (4)
Dental treatment	1 (2)
Other	10 (29)

[a] Pretreatment had been performed in 56/166 (34%) of the treatment group patients and in 36/120 (30%) of the waiting group individuals (odds ratio 1.2; 95% confidence interval 0.70–2.0).

Table 3
Scores of the three verbal rating scales used in this study.[a]

Score	Tinnitus loudness score	Tinnitus annoyance score	Tinnitus change score
0	Inaudible	Absent	Completely disappeared
1	Very faint	Very little	Very much better
2	Faint	Little	Better
3	Moderate	Tolerable	Somewhat better
4	Loud	Moderate	Unchanged
5	Very loud	Strong	Bad
6		Very strong	Worse
7		Extreme	Worst

[a] Tinnitus loudness score: 6-point numeric verbal rating scale of tinnitus loudness. Tinnitus annoyance score: 8-point numeric verbal rating scale of tinnitus annoyance. Tinnitus change score: 8-point numeric verbal rating scale of tinnitus change (Zenner and de Maddalena, 2005).

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Table 4
Standardized, tinnitus-specific interventional procedures.

P1: Tinnitus evaluation: Peripheral audition and central auditory cognition,[a] discussion of the individual disease model[b,c]
P2[d]: Education: Therapeutic principles and planning of the CBT,[e] muscle relaxation therapy,[f] therapy of comorbidities[e]: e.g., sleep training in case of sleep disorders, training of hearing tactics, if necessary fitting of hearing aids
P3: Cognitive defocusing: cognitive processing[g]
P4: Tinnitus coping: tinnitus stressors[h]
P5: Cognitive defocusing: attention refocusing?[i]
P6: Cognitive defocusing: attention diversion by given imaginations[j]
P7: Cognitive defocusing: attention diversion by the patient's own positive imagination[k]
P8: Emotional defocusing: emotional modification[l]
P9: Cognitive defocusing: sensory attention[e]
P10: Tinnitus coping: dealing with stress situations[m]
P11: Functional cognitive handling: avoidance behavior[n,o]
P12: Functional cognitive handling: illness gains[p]
P13: Tinnitus coping: coping with highly significant stress situations[q]
P14: Tinnitus evaluation: cognitive response to the disease[r]
P15: Therapy closure procedure: relapse prevention[s]

[a] Zenner, 1994, 1996.
[b] Zenner et al., 2006.
[c] On the basis of the structured interview results, a manualized version of the sensitization model of tinnitus centralization (Zenner et al., 2006) as well as the clinical, audiological and imaging results.
[d] The education in procedure P2 is based on the structured interview results, a manualized version of the sensitization model of tinnitus centralization (Zenner et al., 2006) as well as the clinical, audiological, and imaging results. All remaining procedures were manualized.
[e] Zenner and Zalaman, 2005.
[f] Conrad and Roth, 2007.
[g] Fritsche et al., 1997, pp 53–57.
[h] Delb et al., 2002a,b, p 104; Fritsche et al., 1997, pp 61–64.
[i] Fritsche et al., 1997, pp 65–70.
[j] Delb et al., 2002a,b, p 104.
[k] Fritsche et al., 1997, pp 73–76.
[l] Fritsche et al., 1997, pp 73–76.
[m] Fritsche et al., 1997, pp 91–93.
[n] e.g. in case of social withdrawal.
[o] Fritsche et al., 1997, pp 79–81.
[p] Fritsche et al., 1997, pp 85–88.
[q] Fritsche et al., 1997, pp 97–99.
[r] Fritsche et al., 1997, pp 103–105.
[s] Fritsche et al., 1997, pp. 109–110.

2.3. Interventions

Treatment consisted of a tinnitus-specific structured CBT in the clinical setting of the structured tinnitus care DMP. Each intervention was carried out on an individual basis. The interventional procedures are listed in Table 4. The structured tinnitus care DMP is based on a standardized diagnosis and therapy procedure considering individual patient characteristics (Fig. 1), and its components have been described previously (Table 5; Zenner and Zalaman, 2005). The essential elements of the structured tinnitus care program were available to all therapists via an interactive online expert system (tinnitus disease manager, Mediceon Tübingen, Germany). All six therapists were physicians or psychologists. With the aid of a benchmarking process, they had received a practical training of 3–12 months in length for both the tinnitus-specific CBT intervention procedures and the structured tinnitus care program.

2.4. Outcomes

The pre-specified primary outcome measure was the tinnitus change score (Zenner and de Maddalena, 2005, Table 3). Secondary outcome measures were the TQS (Goebel and Hiller, 1994), TLS with the 6-point rating scale, and TAS with the 8-point rating scale (Table 3). A data-driven composite of these four variables (CALQ: change, annoyance, loudness, questionnaire), the multivariate u-score (Wittkowski et al., 2004), was pre-specified as the primary endpoint. Together, these variables were used to assess efficacy. Responses based on TQS, TLS, and TAS were calculated as each patient's difference between baseline and completion of therapy. The tinnitus change score was measured at completion of therapy only (Table 3).

2.5. Sample size

Sample size was determined in advance for a one-sided multivariate rank-sum test, to show superiority where no significant harm could be anticipated in stable disease. For a significance level of 2.5%, power of 90%, and an effect size of 0.5, there had to be 92 complete valid observations in each treatment group, if the test was univariate. Few drop-outs could be expected from missing baseline data, and no loss to follow-up would diminish the intention to treat data set (ITT) data set. Multivariate analysis would increase power while correlated results of patients treated by the same therapist would call for a larger sample size. The protocol specified "up to 300 patients" because allocation could not be exactly balanced.

2.6. Allocation

All patients of the first four centers were assigned to the treatment group. All patients of the last-designated center ($n = 120$)

Table 5
Components of the structured tinnitus care disease management program.

Components of the disease management program	Objective
Evidence-based guidelines for therapists	Provides recommendations for tinnitus diagnostics and therapy procedures
Patient training, patient internet platform[a]	Informs and promotes patient education including the rehearsal of techniques for self-management
Therapist information system, "Tinnitus Disease Manager" (interactive online expert system, algorithms, manuals, videos, databases)	Knowledge manager for therapist
Patient treatment plans	Provides evidence-based, individually tailored therapeutic recommendations with estimates of the personal risk profile
Interactive advanced training for therapists	Provides evidence-based medical as well as organizational instructions for the disease management program
Personnel development structure, benchmarking	Allows a consistent vocational and procedure-related training
Standardized patient data record and case record form	Basis for evaluation and for internal and external quality assurance
Quality management, result recording and evaluation	Result evaluation

Essential elements of tinnitus management with the disease management program are comprehensive therapeutic guidelines that are available as an interactive online expert system (tinnitus disease manager). The tinnitus disease manager provides continuously updated online access to the interventional procedures, algorithms, diagnostic and therapeutic guidelines, a comprehensive collection of other aids (standardized case record forms, standardized forms, diagrams, videos, questionnaires, printable information for patient information and training, patient notesheets, resources for patient education, practicing resources for patients), vocational training resources, and extensive databases. In addition, manuals are also available. The interventional procedures exist in the form of manuals. The methods to be applied are found in the program's quality management system (e.g., guidelines, defined procedures and trainings) along with the criteria for monitoring methods and quality. Depending on needs, the therapists participating in the disease management program are trained according to standardized principles for between 3 months and a year in the implementation of the program.
[a] http://www.deukonet-tinnitus-portal.hno-tubingen.de.

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were assigned to the waiting list control group. In this center, some therapists were still specifically training for the tinnitus-specific CBT intervention procedures and the structured tinnitus care DMP, and their patients waited for at least one typical treatment period. The inclusion of the waiting period of these patients in the study allows these patients to represent the waiting/control group. This form of allocation amounted to a quasi-randomization of therapist clusters and precluded masking and concealment of allocation. Allocation could not be exactly balanced either. The waiting group was not enlarged for obvious ethical reasons and because less variance was expected there.

2.7. Statistical methods

First, demographics of treatment groups were described to ensure that they were similar with respect to known predictors of response. The ordinal variable tinnitus side and the dichotomous traits of sex, hyperacusis, and dichotomized tinnitus change were summarized as medians and quartiles. Groups were compared by odds ratios (ORs) from ordinal logistic regression and 95% confidence intervals (CIs). Dichotomous feature comparisons were kept similar with natural cut-offs at 12 months and in the middle of the 8-point scale between "somewhat better" and "unchanged." Age was assumed to be normally distributed, so that the arithmetic means and standard deviations and CIs for the difference between the means of age were given. Tinnitus duration (4–12 months, more than 12 months) and tinnitus quality (whistling, buzzing, low band noise, other) were treated as nominal variables. Pearson's χ^2 for the quality type was used.

Superiority of efficacy was then tested. Only if the first, multivariate rank test was significant were components of the multivariate endpoint tested to describe their contributions. ORs for changes of one point between treated and waiting/control patients were estimated using ordinal logistic regression along with 95% CIs. The ordinal numbers of the primary outcome variable and of the primary and secondary endpoints were summarized as medians and quartiles.

Additionally, effects of known confounders were explored by ordinal logistic regressions. Tinnitus compensation, tinnitus quality, pretherapeutic tinnitus duration, and individual study duration were entered into the model along with all two-way interactions. Variables were selected backwards with P to enter 0.25 and P to leave 0.1. Sensitivity to overfitting was checked by leaving out more variables.

The multivariate rank test was carried out using muStat.rockefeller.edu (Wittkowski et al., 2004). All other statistics were computed using JMP 7.0.1 (SAS Inst. Inc., Cary, NC, 2007).

2.8. Ethics

A complete clinical study protocol was compiled according to the ICH guidelines for good clinical practice (Consolidated Guideline, 1996) and Clinical Trials (General Considerations for Clinical Trials, 1997; Statistical Principles for Clinical Trials, 1998; Choice of Control Group and Related Issues in Clinical Trials, 2000). It was presented to the Institutional Review Board (Independent Ethics Committee) of the University of Tübingen (University of Tübingen Ethics Committee Identifier Number 372004), and no objections were raised. Furthermore, the study was registered in the U.S. NIH clinical study protocol registration system (clinicaltrials.gov; identifier: NCT 00719940).

3. Results

3.1. Participant flow

Recruitment was halted when both group sizes exceeded the minimum calculated, one group size was above the planned 150 and one below, and waiting could not be justified by therapist training any longer. A total of 286 patients participated as ITT patients in the study. Participant flow is presented in Fig. 2. Of these, 166 belonged to the treatment group, and 120 were in the control group.

3.2. Losses and exclusions

Six ITT patients in the therapy group did not complete treatment, two because of accidents unrelated to therapy, one because of depression, one because of a sudden sensorineural hearing loss, and two for nonmedical reasons. Missing values were imputed so that the individual therapeutic effects were set to zero. As such, all 286 patients, 98 women (34%) and 188 men (66%), entered the analyses as ITT patients.

3.3. Recruitment

Eligible patients were recruited at the five centers. At four outpatient clinics, 145, 13, 6, and 2 patients were recruited, respectively, and at one hospital unit, 120 patients were recruited. All patients were recruited between October 2000 and October 2005 and followed for up to one year. Patients in the therapy group attended visits at baseline and for each individualized therapy session, as indicated in Fig. 2. At the end of individual therapy, study endpoint scores were determined. Patients in the control group attended a visit at baseline and waited until study endpoint scores were determined. As a result, the outcome of the intervention group was assessed at a median of 10 weeks (quartiles 7 and 18 weeks) after treatment onset. In the control group, outcome was measured at a median of 24 weeks (quartiles 19 and 29 weeks) after the beginning of the waiting period. Thus, the mean time between pre- and post-measurements in the waiting group was more than two times that of the treatment arm. Multiple cumulative logistic regression presented later, however, of the test scores on treatment

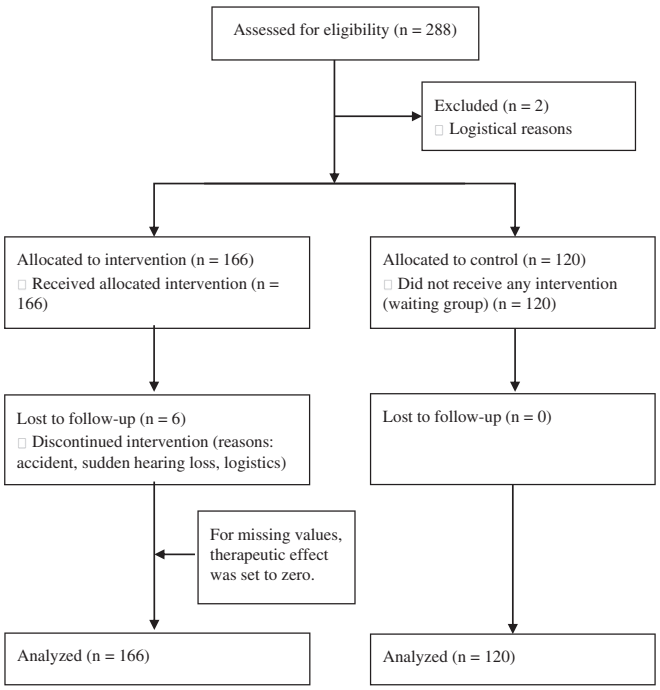

Fig. 2. Flow of patients through trial of structured cognitive-behavioral therapy versus waiting/control group. Diagram includes information about excluded patients and discontinued interventions.

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type revealed that the study arms became comparable by inclusion of the period of time between patient-in and patient-out as a covariate (see also Fig. 4).

3.4. Baseline data

With a median of 49 years, age ranged between 14 and 78 years. Treatment and non-treatment groups were matched at baseline with respect to age and disease severity (as determined by TQS, loudness score, and annoyance score), but not with respect to sex, tinnitus compensation, tinnitus quality, or tinnitus duration (Table 1).

Among the 286 ITT patients, 97/285 (34%) and 188/285 (66%) had suffered continuously from tinnitus for between 4 and 12 months or for more than 12 months, respectively. In 5%, the type was usually a buzzing, in 20%, it was a narrow band noise, and in 47%, it was whistling (86 missing values, Table 1). In 92% (264/286) of all patients, pure tone audiograms and TEOAEs showed a concomitant cochlear sensorineural hearing loss. Audiological tinnitus matching revealed a tinnitus frequency between 125 Hz and more than 10 kHz with a median of 6 kHz. Audiometric tinnitus matching revealed values from 0 dB sound pressure level (SPL), with 0 dB SPL tinnitus level being identical to the hearing threshold, to 31 dB SPL (31 dB above hearing threshold; median 3 dB, quartiles 1 and 7 dB, 373 ears). The loudness in the TLS (Table 1) revealed values between 0 and 5 with a median of 3 (quartiles of 2 and 4). TAS (Table 1) values were 0–7 with a median of 4 and quartiles of 3 and 5. The median TQS was 28 (quartiles 17 and 43).

Regarding noise quality in the groups (46% and 47% whistling) and sex (67% and 63% male, respectively), only minor imbalances could be found between the therapy and control groups. The largest OR in Table 1 arose because 12% of the individuals in the control group had suffered from their tinnitus for less than one year; among the treated individuals, this applied for 50% and required an adjustment in the final evaluation.

3.5. Outcomes and estimation

After treatment, a statistically significant improvement in tinnitus symptoms was demonstrated with the primary outcome measure of tinnitus change score, with the composite endpoint CALQ and with all secondary outcomes measures (TQS, loudness, and annoyance scores) in the treatment but not in the control arm (Fig. 3). Using the tinnitus change score, 84% of the patients in the treatment group showed improvement after treatment, but only 22% did so in the waiting list/control group. When comparing the two groups using the rank-sum test, the tinnitus change score comparison revealed a statistically significant difference, with the treated group showing a significant improvement and the control group showing no significant change (Fig. 3A). Furthermore, the ordinal logistic regression of the tinnitus change score on treatment produced an OR of 3.4 (CI 2.6–4.5). The CI did not include values anywhere near unity, giving strong support of a pronounced tinnitus change. Moreover, only in the treated group did the TQS decrease by around 50% from a median of 27 to 13.5 (Fig. 3B). In addition, the TLS improved from a median of 3 (quartiles 2 and 4) to a median of 2 (quartiles of 1 and 3; Fig. 3C) in treated patients, and the TAS was reduced from a median of 4 (quartiles of 3 and 5) to a median of 1 (quartiles of 1 and 3; Fig. 3D).

Using the multivariate u-score and comparing the treatment arm with the control group using both primary and secondary response criteria, the composite endpoint CALQ showed a significant difference ($P < 0.0001$). The same was true if univariate scores were considered. Multiple cumulative logistic regression of the test scores on treatment type revealed that the interaction between treatment type and individual study duration was not significant ($P = 0.67$) because the tinnitus change score tended to be higher the longer individuals waited (Fig. 4).

Apart from these results, additional data were explored. As already mentioned, groups differed with respect to the factors of tinnitus compensation and quality and pretherapeutic tinnitus and individual study duration. Very early differences in probability of improvement could be attributed to treatment or to such confounders. Thus, these factors and all two-way interactions were entered into a multiple cumulative logistic regression from the tinnitus change score on treatment type. The produced model comprised the four main effects of (i) treatment, (ii) tinnitus duration, (iii) individual study duration, and (iv) tinnitus quality as well as the interaction between tinnitus quality and tinnitus duration. The probability of improving the score by one point in the tinnitus change score was four times higher in the treatment than

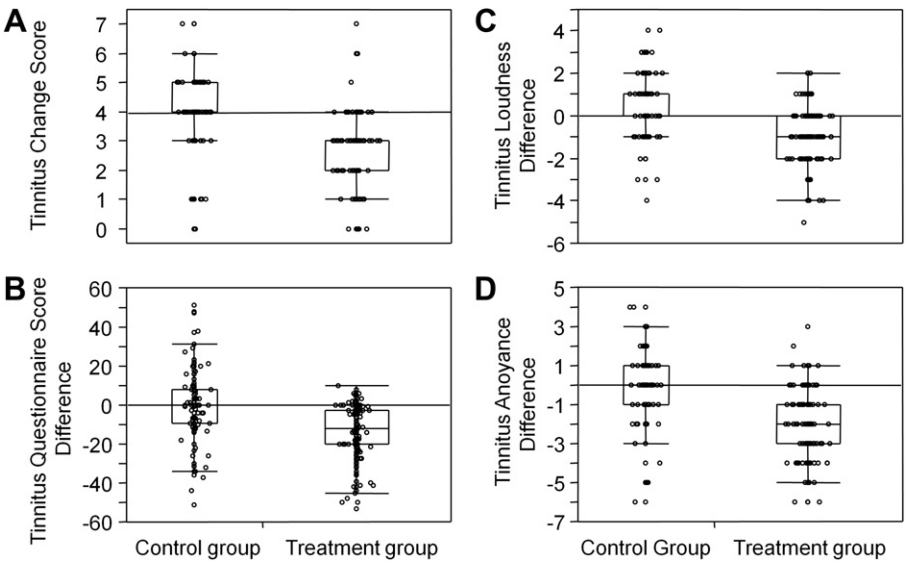

Fig. 3. Box plots of individual treatment effect between baseline and follow-up by group. Effect of structured cognitive-behavioral therapy on treatment outcome. (A) Significantly different changes when measured as tinnitus change score (TCS, 1 to 3 denote improvement, 4: "unchanged"). (B–D) Score differences between patient-in and patient-out, namely significant decreases in (B) tinnitus questionnaire score (TQS), (C) tinnitus loudness (TLS), and (D) tinnitus annoyance (TAS) after treatment but not for the waiting group.

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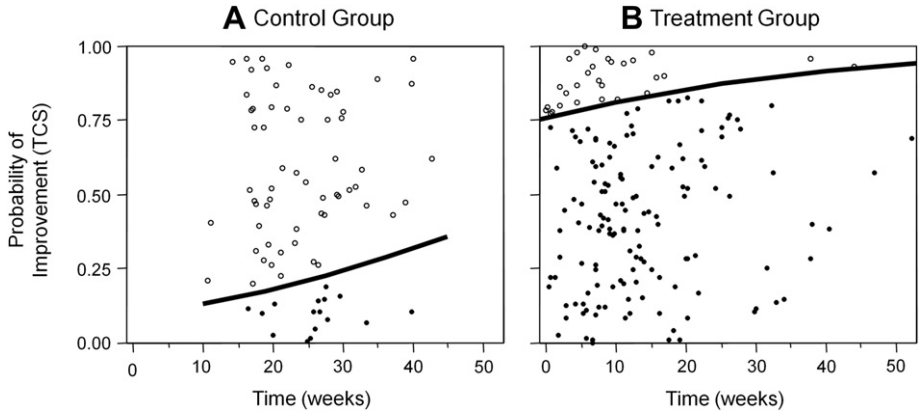

Fig. 4. Time dependence of tinnitus change by group using the tinnitus change score. Improvement probability was higher in the treatment group. A slight spontaneous improvement in the control group was estimated to be higher the longer the wait in (A). (B) Tinnitus change score (TCS) improved the longer therapy lasted in the treatment group. Bold lines indicate probabilities of improvement, i.e., a score below 4. Circles are the single observations plotted at the exact time and at a random ordinate on the correct side of the regression line. Filled symbols indicate a score <4 (improvement). Time in (A): waiting time; time in (B) treatment time.

in the control group. When the tinnitus quality factor was omitted (because there were some very rare tinnitus types), the OR (3.9) remained close to the unadjusted result. This regression model with 4 degrees of freedom reduced the negative log-likelihood by 43–407.

When subdividing patients into the two subgroups, one with a tinnitus duration of 4–12 months and another with a tinnitus duration of more than 12 months, regression analysis showed no significant effect of tinnitus duration on the primary outcome measure and the composite endpoint or the secondary endpoints. Furthermore, in an ordinal logistic regression of tinnitus change score on treatment, the TQS subscores A (auditory perceptive difficulties), E (emotional distress), C (cognitive distress), I (intrusiveness), SL, and SO (SL: sleep disturbances; SO: somatic complaints) measured at baseline were used as explanatory variables. The improvement with therapy (i.e., a significant tinnitus change score improvement) was shown even if patients produced the extremes of the subscores E, C, I, SL, and SO (Table 6). By contrast, high TQS subscores only rarely (7%–8%) improved in the waiting group. As expected, for the subscore A (auditory perceptive difficulties), no interaction with the therapy was identified (Table 7).

When investigating the time-course of the tinnitus change score, improvement increased with duration of therapy (Fig. 4). Of interest, a similar time course was seen in the control group (Fig. 4). Furthermore, a relationship between therapeutic effect and tinnitus severity was observed. With an OR of 1.6, the improvement effect in the tinnitus change score with decompensated tinnitus appeared to be more pronounced than that for a compensated tinnitus.

Table 6
Probability (P) of tinnitus change score to become less than or equal to 3 depending on the subscores of the tinnitus questionnaire score.[a]

Probability (P)	Treatment	Control
P if A = 14	0.69	0.16
P if A = 0	0.81	0.28
P if C = 16	0.78	0.08
P if C = 0	0.78	0.39
P if E = 24	0.78	0.07
P if E = 0	0.78	0.39
P if I = 16	0.71	0.08
P if I = 0	0.85	0.45
P if SL = 11	0.83	0.07
P if SL = 0	0.76	0.32
P if SO = 8	0.88	0.07
P if SO = 0	0.75	0.29

[a] i.e., probability of tinnitus improvement for the two extremes of the observed subscores A = auditory, C = cognitive, E = emotional, I = intrusiveness, SL = sleep, and SO = somatic, by treatment arm as estimated in ordinal logistic regressions.

3.6. Safety and adverse events

During treatment, 40 adverse events were recorded. Thirty patients developed an upper respiratory infection, rhinitis, or sinusitis. Four patients suffered from allergies or eczema and one from dizziness. One individual in the therapy group perceived "unpleasant images." Four patients experienced, accidents unrelated to therapy (2 patients), one exacerbation of a preexisting depression, and one sudden hearing loss. In these patients, the adverse events led to an early discontinuation of therapy (drop-outs), affecting the results as described under losses. Although 39 adverse events were not therapy induced, a treatment-related adverse effect could not be excluded for the minor event "perception of unpleasant images."

4. Discussion

4.1. Generalizability

The results of the present study suggest that tinnitus-specific CBT as part of the structured tinnitus care DMP can be effective as an individual therapy for patients suffering from tinnitus for 4 months or more. Of the patients in the treatment group, 84% reported a significant benefit while only 22% of those in the waiting group showed improvements. The OR for improvement was so large (3.4) and the lower confidence limit so high (2.6) that the result cannot plausibly be attributed to confounding with a center effect. In addition, it cannot be attributed to a lack of masking

Table 7
Median (and quartiles) of outcome measures by arm and odds ratios (ORs) and 95% confidence intervals (CIs) from ordinal logistic regression from change on treatment.

	Treated	Control	OR (CI)
	Median score (quartiles)		
Primary variable			
Tinnitus change score	3 (2–3)	4 (4–5)	3.4 (2.6–4.5)
Secondary variables			
• Goebel and Hiller score	13.5 (7–23)	28 (15–46)	2.0 (1.6–2.5)
• Loudness score	2 (1–3)	3.5 (3–4)	2.2 (1.8–2.8)
• Annoyance score	1 (1–3)	4 (3–5)	2.6 (2.1–3.3)

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because measurements taken two times corroborate the efficacy claim. CBT is a safe therapy: Only one minor adverse event occurred that could not be excluded as therapy related. External validity was high given that biases by the few well-explained drop-outs are unlikely and that the trial was conducted in a pragmatic fashion.

The primary outcome measure, tinnitus change score (Zenner and de Maddalena, 2005), the composite endpoint CALQ, and the secondary endpoints of TQS (Goebel and Hiller, 1994), annoyance score, and loudness score (Zenner and de Maddalena, 2005) improved statistically significantly in the treatment group compared to the waiting/control group. The composite endpoint CALQ consisted of variables that strongly and positively correlated with the treatment effect and with each other. Evaluations carried out according to the study protocol and the retrospective adjustments both led to the same results. A regression to the mean of the pre-therapeutic tinnitus on the outcome in the waiting group seems unlikely.

Classical CBT is characterized by a high therapeutic freedom and variability with iterative adaptation of the procedures (Fritsche and Kröner-Herwig, 1997). As such, the therapeutic process for different patients is not explicitly standardized and can be difficult to compare or reproduce. The present study reduces the problem of comparability and reproducibility by applying standardized interventions. Their application in group therapies had already been evaluated elsewhere in controlled studies (Delb et al., 2002a,b; Fritsche et al., 1997; Kröner-Herwig et al., 1995, 2003; Zenner and Zalaman, 2005). Furthermore, a structuring of the treatment process was achieved by the tinnitus care program, a structured DMP developed specifically for the application presented here (Fritsche and Kröner-Herwig, 1997; Zenner and Zalaman, 2005).

4.2. Limitations

The present study compared a treatment group with a waiting list control. Clearly, no double-blind design was possible in this behavioral treatment study. Nevertheless, patient–therapist interaction in the experimental group was missing with the waiting list controls, a factor that could have led to the outcome's being related to a placebo effect, similar to drug studies. On the other hand, waiting alone may create a strong expectancy for change, which could have conferred at least short-term placebo effects in the waiting list control. Furthermore, some patients may have sought their own therapists or enacted other interventions, which could have yielded some effects that cannot be totally excluded. This possibility corresponds to the observation that the control group also showed an improvement in symptoms in the tinnitus change score but did not improve significantly.

The mean time between pre- and post-measurements in the waiting group was longer than that of the treatment arm. Three results suggest that this difference may not have produced a false-positive efficacy outcome in the present study. First, multiple cumulative logistic regression of the test scores on treatment type revealed that study arms became comparable by inclusion of the period of time between patient-in and patient-out as a covariate. Second, the tinnitus change score increased in the non-treatment arm the longer the individuals waited, indicating that the difference in the observation periods may have contributed only to a negative shift of the efficacy outcome, thus excluding false-positive results. Third, multiple cumulative logistic regression of the test scores on treatment type revealed that the interaction between treatment type and individual study duration was not significant ($P = 0.67$) (Fig. 4). Thus although tinnitus duration may influence treatment response, treatment is the factor that had the predominant effect on efficacy outcomes in models using both as predictors.

Tinnitus evaluation may be criticized because of the choice of outcome variables (Dobie, 1999). Objective methods of measurement are not available, and the measurement of therapeutic success based on self-assessment is therefore the only available measure. For this purpose, visual analog scales have been suggested for tinnitus determination that are analogous with those used for pain measurement (Caffier et al., 2006); however, such scales have not yet been validated for assessing the subjective loudness and annoyance of tinnitus (Goebel and Hiller, 1994). Thus, in the present study, three verbal rating scales and the TQS were used, all of which had been validated on large patient cohorts (Goebel and Hiller, 1994; Jakes et al., 1985; Zenner and de Maddalena, 2005).

The present study did not allow a distinction between possible therapist effect and actual treatment effects. Thus, to minimize differences among therapists, a structured tinnitus care DMP was used. Furthermore, with the aid of a benchmarking process, all therapists had received a practical training of 3–12 months for both the tinnitus-specific CBT intervention procedures and the structured tinnitus care program.

4.3. Interpretation

According to a recently suggested model of tinnitus centralization, cognitive factors may play a key pathophysiological role (Zenner et al., 2006) together with emotional factors. In agreement with Overmier (2002), the main sensitizing factors of a tinnitus stimulus (Zenner et al., 2006) are as follows: (i) the tinnitus is evaluated as harmful (noxious); (ii) the tinnitus induces anxiety; (iii) the tinnitus duration is unpredictable; and (iv) the tinnitus sufferer feels helpless (loss of control) in face of the tinnitus. The cognitive sensitization model can therefore explain why patients may suffer from a progressively worsening tinnitus.

The cognitive-affective model for a complex tinnitus (Hallam et al., 2004; Zenner et al., 2006) matches theoretical principles of CBT (Hofmann et al., 2007). Hallam et al. (1985, 1988, 2004) has already pointed out that tinnitus may result from a lack of habituation and the growing attention to the signal. Habituation is a specific learning process and the opposite of sensitization (Birbaumer and Öhmann, 1993). The sensitization model is also consistent with the ideas of Møller, who postulated similarities with chronic pain processing (Møller, 2003). The mechanisms underlying sensitization are known as a specific learning process involving cortical plasticity. It is therefore reasonable to assume that this learning process can be altered by counteracting learning mechanisms.

Of interest, it has also been suggested that both tinnitus loudness and tinnitus suffering are partially correlated with "emotional distress" and "cognitive distortions" (Hallam et al., 1988, 2004). Cognitive influences are characterized by the tinnitus being perceived as loud, unpleasant, and distracting. A separate study has suggested that the subjective changes in the tinnitus annoyance, tinnitus loudness, and tinnitus change scores may be more emotional and cognitive in nature than being a sensory problem (Zenner and de Maddalena, 2005). The statistically significant improvement of the treatment group in this study therefore may also be the result of a successful desensitization of the tinnitus-related cognition and emotion.

5. Conclusions

In summary, a structured tinnitus-specific CBT using standardized tinnitus-specific interventions could be an effective individual therapy for the treatment of patients suffering from chronic tinnitus.

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Conflict of interest

H.P. Zenner was a shareholder of Mediceon from 2001 to 2002. B. Zenner was a shareholder and officer of Mediceon from 2003 to 2005. S. Pogge was an employee of Mediceon from 2003 to 2004. No other potential conflicts of interest relevant to this article exist.

Acknowledgments

The study was supported by grants from the Ministry of Research and Technology (BMFT, Project “Deutsches Kompetenznetz Tinnitus”) and from Mediceon.

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