Study Protocol and Statistical Analysis Plan

Study Title: Dismantling internet-based cognitive behavioral therapy for tinnitus. The contribution of applied relaxation. A randomized controlled trial

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Background
Tinnitus, characterized by the perception of sound in the absence of an external stimulus, is one example of such a condition. Managing tinnitus is notoriously challenging as there is often not a curable medical cause. The intervention with strongest research evidence is cognitive behavioral therapy (CBT) for tinnitus. CBT is psychological intervention addressing unhelpful thought patterns and emotional reactions caused by tinnitus (Andersson, 2002). Despite the evidence base, accessibility to CBT for tinnitus is limited due to a dearth of healthcare providers with the knowledge and expertise to provide CBT to this population (Bhatt et al., 2016; Henry et al., 2019).

To overcome this barrier, an Internet-based CBT for tinnitus (ICBT; Andersson et al. 2002) has been developed. The efficacy of ICBT has been indicated in nine clinical trials across mainland Europe and the UK (for review see Beukes et al., 2019). However, no previous studies have examined the the importance od different components of CBT program.

Objectives
To seek ways of improving outcomes of ICBT, the aim of this study was twofold. Firstly, to dismantle the whole ICBT package against applied relaxation only. Secondly, to assess the intervention effects across different tinnitus subgroups. To our knowledge, this is the first ICBT trial to investigate the components of ICBT for tinnitus that are most meaningful and compare tinnitus subgroups.

Study Design
A randomized, prospective 2-arm intervention dismantling trial with a 2-month follow-up was undertaken. Participants were randomized to the full ICBT intervention or applied relaxation. During Phase I (8 weeks) the ICBT group was provided the full CBT intervention and the applied relaxation group received the applied relaxation sections. During Phase II (4 weeks), the applied relaxation group was provided the remaining CBT components. This study design, therefore, provided the opportunity to evaluate the intervention effects in two independent groups at three different time points.

Recruitment Strategy
The participants were recruited from the general public using a range of strategies, including promoting the study via tinnitus support groups and the American Tinnitus Association (ATA) between 1 April to 4 May 2020. Further recruitment strategies included the use of social media (e.g., Facebook and Twitter), and also distributing flyers and posters to local health clinics (i.e., primary care physician, audiology, ENT) and communities and put up in clinic waiting rooms. Those interested were directed to the study website (www.tacklingtinnitus.org) where they could read more about the study, the university hosting the study, the research team, and how they could register interest in partaking in the study. Following registration, an online screening questionnaire (i.e., baseline assessment at T0) was completed. Participants were informed of their right to withdraw at any stage without penalty.

Study Population
The eligibility *inclusion criteria included*: adults, aged 18 years and over; living in the US; the ability to read and type in English; access to a computer, the internet and the ability to email; experiencing tinnitus for a minimum period of three months; any configuration of hearing levels (normal or any degree of hearing loss) and any use of hearing devices (using or

not using hearing aids); and participants were included if they described a need for a tinnitus intervention and not based on their tinnitus outcome scores.

*The exclusion criteria were r*eporting pulsatile, objective, or unilateral tinnitus, which had not been investigated medically or tinnitus still under medical investigation; reporting any major medical condition or treatment that would prevent undertaking this intervention; and undergoing any tinnitus therapy concurrent with participation in this study.

Participants were required to provide online consent to participate. Eligibility was determined by a two-stage process. Firstly, participants completed an online screening questionnaire, which included demographic information, health and mental health-related questions, and standardized outcome measures. After this, a telephone interview was conducted during which the researcher rechecked eligibility and provided the opportunity for potential participants to ask any questions related to the study. The study procedures were explained, and motivational interviewing was done to encourage participants to commit and engage in the intervention. Any participants with a score of 15 or more on the Patient Health Questionnaire–9 (PHQ-9) or indicated self-harm on question 10 received an additional phone consultation from a clinical psychologist on the research team. This call ensured that their depression was being managed and that they had the required resources and were not in any danger of self-harm. If the psychologist was assured that their depression was well managed they were eligible to participate in the study.

Participants meeting the inclusion criteria were divided into three subgroups.

i. Those with significant levels of tinnitus distress with scores of 25 or above on the Tinnitus Functional Index (TFI) which was used to measure tinnitus severity (i.e., high tinnitus severity group).
ii. Due to numerous participants scoring below 25 and requesting help with their tinnitus, those with low tinnitus severity (<25 on the TFI) were included as a separate subgroup (i.e., low tinnitus severity group).
iii. Those with high depression scores > 10 on the PHQ-9 or those answering positively for question 10, were added as a further subgroup (i.e., significant depression group).

Sample Size, Power, and Attrition

Sample size calculations were performed using the SampSize app for superiority parallel groups. Power was 90%; α was 0.025; and the estimated SD was 20 points, as indicated by the preceding pilot trial (Beukes et al., 2021b). The mean difference was set to 13 points, as indicated during the validation of the TFI (Meikle et al., 2012) to be a clinically significant change in scores. Thus, 51 participants were required for each arm. To ensure sufficient power, calculations for the larger sample were followed with the aim of recruiting 63 participants per arm to inflate for possible missing data.

Randomization

Participants meeting the inclusion criteria were randomly assigned in the ratio of 1:1 after being stratified for tinnitus (<25 or ≥25 on the TFI) and depression (<10 or ≥10 on the PHQ) and enrolled to either the ICBT or applied relaxation group using a computer-generated randomization scheduled by an independent research assistant in blocks of varying sizes. Participants and investigators could not be blinded to group allocation due to the nature of the intervention. The researchers were however blinded during data analysis. Participants were informed of their group allocation and when the intervention would commence by the principal investigator.

Intervention

The study employed a structured intervention based on a CBT for tinnitus program (Andersson & Kaldo, 2004; Beukes et al., 2021). This intervention was originally developed in Sweden (Andersson et al., 2002), and was later adapted into an interactive e-learning version for a UK population (Beukes, et al., 2016). To ensure suitability for a US population, the intervention was further modified with linguistic and cultural adaptions, such as lowering the readability to below the recommended 6th English reading grade level, (Beukes et al., 2020a; Manchaiah et al., 2020b). The full program consists of 22 modules with explanatory videos, weekly homework assignments, worksheets and quizzes (Beukes et al., 2021). The intervention platform (Vlaescu et al., 2016) was housed in the US at Lamar University to comply with the needed data protection regulations. Prior to this trial, acceptability and functionality of this intervention for a US population were ensured (Manchaiah, et al., 2020a) and the intervention was piloted for a US population (Beukes et al. 2021a). Guidance was provided by an audiologist throughout the intervention. This included introducing the module content, monitoring progress, providing feedback on worksheets completed, outlining the content of new modules, answering questions, and encouraging questionnaire completion. Participants who were not engaging were contacted (messages/ text/ phone) to encourage engagement and discuss possible barriers, and an encrypted 2-way messaging system within the ePlatform was used to communicate with participants. Although psychologists have traditionally guided CBT interventions, tinnitus management is generally delivered by audiologists (Henry et al., 2019). Thus, an audiologist provided guidance to participants to maintain consistency with previous English trials using this intervention (Beukes et al., 2018, 2021b).

The groups accessed the intervention via a secure login, each group accessing different elements of the intervention along with different schedules as seen in Table 1. Both groups were asked to spend around 10 minutes a day practicing the suggested exercises and completing worksheets to monitor their progress.

Table 1. The Intervention schedule for each group

Week	**ICBT group schedule**	**Applied relaxation group schedule**
Phase I	**22 modules**	**10 modules**
1	Program outline Tinnitus overview	Program outline Tinnitus overview
2	Deep relaxation Positive imagery Sound enrichment	Deep relaxation Positive imagery
3	Deep breathing Views on tinnitus Sleep guidelines	Deep breathing
4	Entire body relaxation Shifting focus Improving focus	Entire body relaxation
5	Frequent relaxation Thought Patterns Increasing sound tolerance	Frequent relaxation
6	Relaxing when stressed or upset Challenging thoughts Listening tips	Relaxing when stressed or upset
7	Relaxation routine	Being mindful

	Listening to tinnitus	
8	Summary Future planning	Relaxation routine
Phase II		
9	N/A	Views on tinnitus Thought patterns Sound enrichment
10	N/A	Sleep guidelines Challenging thoughts Improving focus
11	N/A	Shifting focus Listening to tinnitus Increasing sound tolerance
12	N/A	Listening tips Summary Future planning

Measures

Data were collected online at baseline (T0); after the ICBT group completed the full ICBT intervention and the applied relaxation group completed only the relaxation part (T1); for the applied relaxation group after they completed the full ICBT intervention and compared the T1 results for the ICBT group (T2); and at 2-month post-intervention for both groups (T3).

A demographic questionnaire was used to establish health-related and tinnitus-specific information at baseline (T0). A series of primary and secondary outcome measures were administered at baseline as well as during post-intervention.

Primary Outcome Measure

The primary outcome measure was tinnitus severity as measured by the TFI (Meikle et al., 2012). It was selected over other tinnitus questionnaires as it was specifically developed to measure tinnitus severity and assess responsiveness to treatment and for comparison purposes with similar trials in the UK and the US (Beukes et al., 2017, 2018, 2021b).

Secondary Outcome Measures

The following secondary measures were incorporated to assess commonly reported tinnitus-related difficulties:

- The Generalized Anxiety Disorder–7 (GAD-7; Spitzer et al., 2006) assessed symptoms of generalized anxiety disorder.
- The PHQ-9 (Spitzer, Kroenke, Williams, 1999) indicated symptoms of depression.
- The Insomnia Severity Index (ISI; Bastien, Vallières, & Morin, 2001) assessed the presence of insomnia.
- The Tinnitus Cognitions Questionnaire (TCQ; Wilson & Henry, 1998) was used to measure negative tinnitus cognitions.
- The EQ-5D-5L (Herdman et al., 2011) measured general health-related quality of life.
- The Tinnitus and Hearing Survey (THS; Henry et al., 2015) was used as a short measure to identify participants' tinnitus severity, hearing disability, and hyperacusis.

Intervention Variables

Intervention compliance was assessed by determining retention rates and compliance in completing outcome questionnaires. Intervention engagement was assessed by the number of

logins, the number of modules opened, and the number of messages sent during the intervention.

Statistical Analysis Plan

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 26.0. All statistical tests were 2-tailed with an alpha set to .05. For transparency, both an intention-to-treat approach including all participants, and a completers-only analysis was undertaken for comparison purposes. For the intention-to-treat model, an imputation analysis was undertaken. Missing data were handled through multiple imputations using the *Markov Chain Monte Carlo* approach. The analysis thus included all participants at each time point.

The primary study outcome was a change in TFI score between groups at post-intervention (T1). Secondary study outcomes were changes in secondary outcomes between groups at T1. According to recommendations for statistical analysis of internet interventions (Hesser, 2015) effect sizes, Linear Mixed Effects Models (LMM), and the Reliable Change Index (RCI) was used to assess the outcomes. Changes from baseline to post-intervention were compared within and between groups using the standardized mean differences (Cohen's *d*) for all primary and secondary outcomes using the observed data. Effect sizes of $d = 0.20$ represent small effect sizes; those of $d = 0.50$, medium effect sizes; and those equal or greater than $d = 0.80$, large effect sizes (Cohen, 1992).

The LMM, which provided unbiased results in the presence of missing data (using all available data) was applied to analyze the intervention effect accounting for the repeated measurements. An unstructured repeated effect and identify random effects covariance structure provided the best model fit based on the Akaike's Information Criterion (AIC). Time was treated as a repeated and fixed effect. Restricted maximum likelihood estimation was applied. The Type III F test sums of squares from the LMM are presented. As a sensitivity analysis, baseline tinnitus severity was initially added as a covariate. As it had no significant effect on the results, it was removed from the model. Subgroup analysis was performed for the three pre-defined subgroups to compare outcomes between them.

The RCI (Jacobson & Truax, 1991) was used as a standardized way of calculating clinical significance for the TFI as the primary outcome. This was calculated using the mean pretest-posttest score difference, the pretreatment standard deviation (26.00), and a test-retest reliability coefficient of 0.78, and as reported in the validation study (Meikle et al., 2012).

Sample Characteristics

Descriptive statistics including gender, age, ethnicity, race, tinnitus duration, hearing aid use, and professionals consulted, ease of computer use, veteran status, education, and employment status were used to describe the sample. The mean and standard deviation were reported for each outcome measure at each time point. Descriptive statistics were also used to assess the sample and intervention engagement including the number of logins and modules opened. A Chi-square test of independence was used to identify group differences regarding engagement and compliance rates.

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