Study Protocol and Statistical Analysis Plan

Study Title: Internet-based Cognitive Behavioral Therapy for tinnitus in Spanish: A global feasibility trial

Clinical trial registration: NCT04335929 on April 06, 2020.

Funding: This study was partly funded by the National Institute on Deafness and Communication Disorders (NIDCD) of the National Institute of Health (NIH) under the award number R21DC017214.

Ethical approval: Institutional Review Board at Lamar University, Beaumont, Texas, US (IRB-FY20-200).

Document Date: June 24, 2021

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). However, no previous trials on Spanish population exist.

Objectives

The aim of the present study was to run a small-scale study to inform feasibility of ICBT in Spanish to inform the protocol of a implementing a larger randomized clinical trials (RCT). The specific objects were to investigate the recruitment, compliance, engagement, acceptance, and outcome feasibility in reducing tinnitus distress and tinnitus associated problems, using ICBT for Spanish speakers with tinnitus.

Study Design

A single-group pretest posttest design was used to determine the feasibility of ICBT for Spanish communities and refine the protocol for larger studies. This was intended to be an initial small-scale study (n =32) without a control group to test the protocol prior to allocating resources to a larger scale study. Such studies are an important initial part of clinical trials designs for complex interventions and considered as the Phase 1 trial.

Intervention

The ICBT intervention content was based on a CBT self-help program originally developed in Swedish (Andersson & Viktor, 2004). This intervention has been translated into German (Jasper et al., 2014) and English (Abbott, et al., 2009) and adapted into an interactive 8-week interactive e-learning version (Beukes, et al., 2016). For the purposes of this study the intervention was translated into Spanish, ensuring readability at below the recommended 6th-grade level (Beukes, et al., 2020) and functionality of the platform housed in the US was established (Manchaiah, et al., 2020a). The ICBT program employed 22 modules with videos, worksheets and quizzes (Beukes et al., 2021a).

To minimize the resources required, on-support guidance was offered to participants. There was an encrypted two-way messaging system enabling participants to ask questions about the program. These messages were monitored by a Spanish-speaking doctoral audiology student who responded in Spanish. If required, further support was available from a specialist tinnitus audiologist or a licensed CBT therapist.

Outcome Measures

The primary outcome was Tinnitus severity as measured by the Tinnitus Functional Index (TFI) (Meikle et al., 2012). Secondary outcomes included measures of anxiety, depression, insomnia, tinnitus cognitions, hearing-related difficulties, and health-related quality of life. Spanish translations (Manchaiah et al., 2020b) of all outcome measures are listed below.

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.

To monitor participants tinnitus severity while undertaking the intervention, the screening version of the Tinnitus Handicap Inventory (THI-S; Newman et al, 2008) was completed weekly during the course of the 8 week intervention. If scores increased by more than 10 points between two consecutive weeks, the participant was contacted to discuss presenting difficulties. Participants were also monitored weekly by a newly developed Tinnitus Qualities Questionnaire (TQQ; Beukes et al., 2021a). The TQQ measures psychoacoustic tinnitus qualities such as pitch, loudness, and the number of tones heard.

Online questionnaires were used throughout the study. All the measures were completed pre- and post-intervention, and at two-month follow-up. To maximize retention, 3 electronic reminders were sent to participants who had not completed questionnaires.

Recruitment

We aimed to recruit participants across the globe without any geographical barrier. To recruit Spanish speakers, a range of strategies were used to disseminate information, including social media (Facebook and Twitter), emails, forums. As uptake was low a company "TrialFacts" were contracted to boost recruitment. The main recruitment period was between 1 March to 20 April 2020. Those interested were directed to the study website, where all the information was available to read in Spanish regarding what the study entailed and how to register. Study eligibility was determined as follows:

- Spanish speakers, adults, aged 18 years and over from any location;
- Access to a computer, the internet and the ability to email;
- Experiencing tinnitus for a minimum period of three months;
- A tinnitus severity score of 25 or greater on the TFI indicating the need for an intervention;

- Not undertaking any other therapies or interventions that may interfere with the current study; and
- Not presenting with any serious health conditions that may prevent undertaking the intervention.

Statistical Analysis Plan

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 26.0. The study outcomes of interest were retention, feasibility, and effect size at post-intervention. For all analyses, the goal of this pilot was to estimate the pre-post-test effect size for all primary and secondary outcomes; however 2-sided *p*-values using alpha = 0.05 are also reported. Missing data were handled through multiple imputation using the Markov Chain Monte Carlo approach as they were missing at random (Little's MCAR test $X^2 = 17.50$ (24) = .83). For comparison purposes a completer's only analysis was also done. The data that support the findings of this study are openly available in Figshare at http://doi.org/10.6084/m9.figshare.13718896.

Effect Sizes and Statistical Modelling

Effect sizes (Cohen's *d*) at post-intervention were calculated by dividing the differences in pre- and post-intervention means by the pooled standard deviations. The reliable change index (RCI) (Jacobson & Truax, 1991) was used as a means of calculating clinical significance for the TFI as the primary outcome. This was calculated using the mean pretest posttest score difference, the pre-intervention standard deviation, and a test-retest reliability coefficient of 0.78, and as reported in the validation study (Meikle et al, 2012). Finally, linear mixed models (LMM) using maximum likelihood with random intercept for participants were used to account for repeated measures and incorporate all available data points in the analysis. The models were used to determine the effect of the pre-intervention scores on follow-up scores. The LMM induces a scaled identity covariance structure. Bonferroni-corrected pairwise post hoc tests were applied to determine which timepoints were significantly different, for each variable.

Sample Characteristics

Descriptive statistics including gender, age, tinnitus duration, hearing aid use, and professionals consulted, 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 describe intervention adherence and engagement including the number of logins and modules read.

References

Abbott, J. M., Kaldo, V., Klein, B., Austin, D., Hamilton, C., Piterman, L., & Andersson, G. (2009). A cluster randomised controlled trial of an Internet-based intervention program for tinnitus distress in an industrial setting. *Cognitive Behaviour Therapy, 38*(3), 162-173. http://doi:10.1080/16506070902763174

Andersson, G., & Kaldo, V. (2004). Internet-based cognitive behavioral therapy for tinnitus. *Journal of Clinical Psychology, 60*(2), 171-178. https://doi.org/10.1002/jclp.10243

Andersson, G., Strömgren, T., Ström, L., & Lyttkens, L. (2002). Randomized controlled trial of Internet-based cognitive behavior therapy for distress associated with tinnitus. *Psychosomatic Medicine, 64*(5), 810-816. http://doi:10.1097/01.psy.0000031577.42041.f8

Bastien, C. H., Vallières, A., & Morin, C. M. (2001). Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Medicine, 2*(4), 297-307. http://doi: 10.1016/s1389-9457(00)00065-4

Beukes, E. W., Vlaescu, G., Manchaiah, V., Baguley, D. M., Allen, P. M., Kaldo, V., & Andersson, G. (2016). Development and technical functionality of an Internet-based intervention for tinnitus in the UK. *Internet Interventions, 6*, 6-15. http://doi:10.1016/j.invent.2016.08.002

Beukes, E. W., Allen, P. M., Manchaiah, V., Baguley, D. M., & Andersson, G. (2017). Internet-based intervention for tinnitus: Outcome of a single-group open trial. *American Academy of Audiology, 12*(4), 340-351. http://doi:10.3766/jaaa.16055

Beukes, E. W., Baguley, D. M., Allen, P. M., Manchaiah, V., & Andersson, G. (2018). Audiologist-guided Internet-based cognitive behavior therapy for adults with tinnitus in the United Kingdom: A randomized controlled trial. *Ear and Hearing, 39*(3), 423-433. http://doi:10.1097/AUD.0000000000000505

Beukes, E. W., Fagelson, M., Aronson, E. P., Munoz, M. F., Andersson, G., & Manchaiah, V. (2020). Readability following cultural and linguistic adaptation of an Internet-based intervention for tinnitus for use in the United States. *American Journal of Audiology*, *29*(2), 97-109. https://doi.org/10.1044/2019_AJA-19-00014.

Beukes, E., Andersson, G., Manchaiah, V., & Kaldo, V. (2021a). *Cognitive behavioral therapy for tinnitus.* San Diego, USA: Plural Publishing Inc.

Beukes, E.W., Andersson, G., Fagelson, M., Manchaiah, V. (2021b). Audiologist-supported Internet-based Cognitive Behavioral Therapy for Tinnitus in the United States: A Pilot Trial. American Journal of Audiology, In Press.

Bhatt, J. M., Lin, H. W., & Bhattacharya, N. (2016). Prevalence, severity, exposures, and treatment patterns of tinnitus in the United States. *JAMA Otolaryngology Head and Neck Surgery,* 142(10), 959-965. http://doi:10.1001/jamaoto.2016.1700

Henry, J. A., Griest, S., Zaugg, T. L., Thielman, E., Kaelin, C., Galvez, G., & Carlson, K. F. (2015). Tinnitus and Hearing Survey: A screening tool to differentiate bothersome tinnitus from hearing difficulties. *American Journal of Audiology, 24*(1), 66-77. http://doi:10.1044/2014_AJA-14-0042

Herdman, M., Gudex, C., Lloyd, A., Janssen, M., Kind, P., Parkin, D., Bonsel, G., & Badia, X. (2011). Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Quality of Life REsearch, 22*(7), 1727-1736. http://doi:10.1007/s11136-011-9903-x

Jacobson, N. S., & Truax, P. (1991). Clinical significance: A statistical approach to defining meaningful change in psychotherapy research. *Journal of Consulting and Clinical Psychology, 59*(1), 12-19. http://doi:10.1037//0022-006x.59.1.12

Jasper, J., Weise, C., Conrad, I., Andersson, G., Hiller, W., & Kleinstäuber, M. (2014). Internet-based guided self-help versus group cognitive behavioral therapy for chronic tinnitus: A randomized controlled trial. *Psychotherapy and Psychosomatics*, 83(4), 234-246. http://doi: 10.1159/000360705

Manchaiah, V., Vlaescu, G., Varadaraj, S., Aronson, E. P., Fagelson, M., Munoz, M. F., Andersson, G., & Beukes, E. W. (2020a). Features, functionality, and acceptability of Internet-based cognitive behavioral therapy for tinnitus in the United States. *American Journal of Audiology*, 1-15.

Manchaiah, V., Muñoz, M. F., Hatfield, E., Fagelson, M. A., Parks Aronson, E., Andersson, G., & Beukes, E. (2020b). Translation and adaptation of three English tinnitus patient-reported outcome measures to Spanish. *International Journal of Audiology*, 59(7), 1-6. http://doi:10.1080/14992027.2020.1717006

Meikle, M. B., Henry, J. A., Griest, S. E., Stewart, B. J., Abrams, H. B., McArdle, R., Myers, P. J., Newman, C. W., Sandridge, S., Turk, D. C., Folmer, R. L., Frederick, E. J., House, J. W., Jacobson, G. P., Kinney, S. E., Martin, W. H., Nagler, S. M., Reich, G. E., Searchfield, G., . . . Vernon, J. A. (2012). The tinnitus functional index: development of a new clinical measure for chronic, intrusive tinnitus. *Ear and Hearing, 33*, 153-176 http://doi:10.1097/AUD.0b013e31822f67c0

Newman, C., Sandridge, S., & Bolek, L. (2008). Development and psychometric adequacy of the screening version of the tinnitus handicap inventory. *Otology & Neurotology, 29*(3), 276-281. http://doi:10.1097/MAO.0b013e31816569c4.

Spitzer, R. L., Kroenke, K., & Williams, J. B. (1999). Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. *JAMA, 282*(18), 1737-1744. http://doi:10.1001/jama.282.18.1737

Spitzer, R. L., Kroenke, K., Williams, J. B. W., & Löwe, B. (2006). A brief measure for assessing generalized anxiety disorder: The GAD-7. *Archives of Internal Medicine, 166*(10), 1092-1097. http://doi: 10.1001/archinte.166.10.1092.

Wilson, P., & Henry, J. (1998). Tinnitus Cognitions Questionnaire: Development and psychometric properties of a measure of dysfunctional cognitions associated with tinnitus. *International Tinnitus Journal, 4*(1), 23-30.