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Official Title of the Study:

Efficacy and Safety of Cognitive Behavioral Therapy, Tones Stimulator in Patients With Subjective Tinnitus: Prospective, Multi-center, Randomized, Single Blind (Subject), Parallel, Superiority, Confirmatory Trial

NCT Number: N/A

Date of the Document: July 20, 2023

SCIENTIFIC BACKGROUND

Tinnitus, characterized by the perception of sound without external stimuli, affects a significant portion of the population and can lead to psychological distress and functional impairments. The prevalence of tinnitus increases with age, and it is often described as ringing, buzzing, or hissing sounds in one or both ears. Current treatments include medication and sound therapy, but there is a need for more effective interventions. Cognitive behavioral therapy (CBT) has been shown to be effective in managing tinnitus by addressing negative thoughts and behaviors associated with the condition.

CBT, originally developed by Beck in the 1950s, integrates cognitive therapy and behavioral techniques to manage conditions like depression and anxiety. It is based on the concept that unrealistic thoughts and negative beliefs lead to various negative emotions and behavioral impairments. By correcting these cognitive distortions through counseling and education, individuals can develop more positive and realistic thinking patterns, reducing negative emotions and behavioral issues. CBT has been widely used for conditions such as insomnia, chronic pain, and anxiety disorders, and its effectiveness in improving quality of life is well-documented.

In the context of tinnitus, CBT is particularly beneficial as it helps modify the patient's reaction to tinnitus, reducing its impact on daily life. Studies have consistently shown that CBT can significantly decrease tinnitus-related distress, improve emotional well-being, and enhance quality of life. For instance, research involving internet-based CBT has demonstrated comparable efficacy to traditional face-to-face CBT, offering a convenient and accessible treatment option for tinnitus sufferers.

Sound therapy is another approach used to alleviate tinnitus symptoms. It aims to reduce the contrast between tinnitus and silence, thereby decreasing the perception of tinnitus. Sound therapy can involve various types of sounds, such as white noise or nature sounds, and is often used in conjunction with CBT to enhance its effectiveness. Mobile apps have become increasingly popular for delivering sound therapy due to their accessibility and flexibility, allowing patients to customize their treatment based on personal preferences.

The integration of CBT and sound therapy into mobile apps offers a promising solution for managing tinnitus. These apps provide tailored interventions that can be accessed conveniently, making them an attractive option for individuals seeking to manage their tinnitus symptoms effectively. By leveraging the strengths of both CBT and sound therapy, such apps aim to improve the quality of life for tinnitus sufferers by reducing psychological and physical functional impairments associated with the condition.

OBJECTIVES

The purpose of this study is to evaluate the efficacy and safety of CBT based digital therapeutics,

in reducing psychological and physical functional impairments caused by subjective tinnitus. This prospective, randomized, single-blind (participant), parallel-design, superiority, confirmatory trial aims to assess whether CBT and sound therapy software can effectively alleviate the distress associated with tinnitus by providing tailored CBT and sound therapy to patients.

DESIGN

This study is designed as a prospective, multicenter, randomized, single-blind (participant), parallel-design, superiority, confirmatory trial. It aims to evaluate the efficacy and safety of a CBT based digital therapeutics, in reducing psychological and physical functional impairments caused by subjective tinnitus. Participants will be randomly assigned to either the intervention group using CBT based digital therapeutics or the control group receiving conventional CBT educational materials. The trial will assess changes in Tinnitus Handicap Inventory (THI) scores and other relevant outcomes over a period of 6 weeks.

METHODS

Participants are selected based on criteria including being aged 19 or older, having chronic tinnitus for more than three months, a THI score between 18 and 77, and the ability to use internet and applications. Exclusion criteria include objective tinnitus, middle ear infections, and other psychiatric conditions. The intervention involves using CBT based digital therapeutics, while the control group receives conventional CBT educational materials. The trial evaluates changes in THI scores and other relevant outcomes over six weeks.

STATISTICAL ANALYSIS PLAN

Statistical tests are conducted at a significance level of 5% or less, using two-sided tests. Descriptive statistics for continuous variables include mean, standard deviation, median, minimum, and maximum, while categorical variables are summarized by frequency and percentage. If data do not meet the assumption of normality, non-parametric methods like the Wilcoxon signed-rank test are used instead of parametric methods like the paired t-test, with normality assessed using the Shapiro-Wilk test, Kolmogorov-Smirnov test, or Q-Q plots. The latest version of R is used for statistical analysis, but other software can also be employed.

The analysis groups are defined as follows: the Full Analysis (FA) set includes all participants who have used the medical device at least once and undergone efficacy evaluation; the Per Protocol (PP) set consists of participants from the FA set who completed the trial without major protocol deviations; and the Safety Analysis Set includes all participants who have used the medical device at least once. Demographic information collected for the FA set includes age, height, weight, gender, smoking status, and alcohol consumption.

The primary efficacy variable is the change in Tinnitus Handicap Inventory (THI) total score from baseline to 6 weeks, analyzed using ANCOVA to compare groups while adjusting for baseline THI

and stratification factors. Secondary efficacy variables include changes in THI subscales, Tinnitus Functional Index (TFI), Visual Analog Scale (VAS) for negative emotions and thoughts, Beck Depression Inventory (BDI), and Beck Anxiety Inventory (BAI). Each secondary efficacy variable is analyzed using descriptive statistics at baseline and at 2, 4, and 6 weeks, with paired t-tests or Wilcoxon signed-rank tests used within groups and two-sample t-tests between groups. Repeated Measures ANOVA or linear mixed models can be used to assess changes over time.

Safety evaluation includes reporting adverse events, assessing vital signs using paired t-tests or Wilcoxon signed-rank tests, and analyzing physical and laboratory findings with paired t-tests for continuous variables and McNemar's test for categorical variables. Missing data are handled using the Last Observation Carried Forward (LOCF) method for the FA set, with available data used as is for other analyses.