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Original Article

Impact of reduction of tinnitus intensity on patients' quality of life

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Abstract

Objective: Assess the impact of a reduction of tinnitus intensity achieved through sound stimulation during sleep on the improvement in the patients' quality of life. *Design*: Acoustic stimuli consisted of a highly customized sound that reproduced the spectral and intensity characteristics of the tinnitus in each patient. This stimulus was uploaded into a portable electronic device and delivered through customized ear buds during sleep, every night for three months. *Study sample*: Twelve patients with subjective idiopathic chronic tinnitus were studied. *Results*: Results were assessed through: (1) the measurement in dB SPL of tinnitus intensity reduction over time; (2) the results of three psychometric tests: Tinnitus handicap inventory (THI), Tinnitus reaction questionnaire (TRQ), Tinnitus functional index (TFI); and (3) a Visual analog scale (VAS) for tinnitus annoyance. After three months of treatment, we observed an average decrease in tinnitus intensity of 14.1 dB SPL ($p < 0.001$), implying a 62% reduction of the perceived sound. This improvement was followed by a statistically significant decrease of TRQ (78%), THI (65%), and TFI (77%). *Conclusions*: These results suggested that the intensity reduction achieved through the protocol used in this study had a direct impact on the improvement in the patients' quality of life.

Key Words: Sound stimulation; sleep; tinnitus handicap inventory; tinnitus reaction questionnaire; tinnitus functional index

Subjective idiopathic tinnitus is a widespread disabling condition, with a prevalence estimated at 10–15% (Henry et al, 2005), seriously affecting the quality of life in 1–2% of the population (Pilgramm & Rychalik, 1999). The postulated trigger for tinnitus pathogenesis is the disregulation of the central auditory processing induced by altered cochlear inputs (Jastreboff, 1990). In most cases, damage to outer hair cells in particular cochlear regions leads to a reduction of spontaneous activity in related nerve fibers, and an imbalance in excitatory and inhibitory networks (Eggermont & Roberts, 2004), which leads to hypersensitivity and hyperactivity in the neurons involved. Hyperactivity may also be the result of reorganization of the cortical tonotopic map after cochlear damage, which induces a release from efferent inhibition at the characteristic frequencies that lose cortical representation (Robertson & Irvine, 1989; Rauschecker, 1999; Eggermont & Komiya, 2000; Noreña & Eggermont, 2003). Increase in spontaneous firing rate has been found at different levels of the auditory pathway: the dorsal cochlear nucleus (Brozoski et al, 2002), inferior colliculus (Mulders & Robertson, 2009), and auditory cortex (Noreña & Eggermont, 2005). Because the brain is not able to discern if this abnormal incoming flux of information is related to real environmental sound, a 'phantom sensation' (tinnitus) may be created (Jastreboff, 1990).

The subjective idiophatic tinnitus may be the result of neural plasticity, and anomalies may develop because of decreased input from the ear, deprivation of sound stimulation, overstimulation or yet unknown factors (Jastebroff, 1990). Since most forms of severe tinnitus are caused by functional changes, it should be possible to reverse it with sound treatment, taking advantage of the plastic properties of the brain (Pedemonte et al, 2010). The use of customized acoustic stimuli is supported by recent studies (Noreña & Eggermont, 2005; Schaette et al, 2010). Different strategies are currently in use, i.e. notched music (Pantev et al, 2012); customized music tracks with or without white noise masking (Neuromonics Tinnitus Treatment, Wazen et al, 2011); pure tones with phase

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shifting (Phase Shifting Treatment, Vermeire et al, 2007); amplitude and frequency modulated sounds (S-tones, Reavis et al, 2012).

In a previous pilot study, our team demonstrated that stimulation applied during sleep with the specific spectral and intensity characteristics of each patient's tinnitus, was effective in reducing tinnitus intensity (Pedemonte et al, 2010). Moreover, by using a sound that matches the patient's perception, a new way of monitoring the evolution of tinnitus intensity was developed providing the physician with a tool for the assessment of the treatment results. However, no data were obtained regarding the impact of the reduction in the tinnitus intensity on the quality of life.

Currently, there is no clear evidence that establishes a link between the changes in tinnitus intensity along treatment and improvement in quality of life. The objective of the present study was to analyse whether the reduction in the intensity of tinnitus achieved through sound stimulation during sleep correlates with an overall improvement of the patient's quality of life. With that aim, results of intensity reduction and psychological assessment of tinnitus were compared.

Methods

Forty-four patients suffering from tinnitus were evaluated at the beginning of this study. According to the criteria of inclusion and exclusion, twelve participants were selected (seven females, five males; ages between 21 and 64). The inclusion criteria were: (1) patients from 18 to 70 years old with unilateral or bilateral subjective idiopathic tinnitus, (2) experiencing tinnitus for more than six months, and (3) THI score above 17. The exclusion criteria included patients that demonstrated: (1) objective or subjective secondary tinnitus, (2) hearing loss of 50 dB hearing threshold level (HTL) or worse in more than two frequencies of the audiogram, (3) patients that had undergone other treatments for tinnitus in the past year, (4) current use of hearing aids, (5) use of psychoactive drugs, (6) depression (Hamilton scale test above 13), and (7) sleep disorders other than those provoked by the tinnitus itself. Patients with sleep disturbances such as apnea, restless legs syndrome, narcolepsy, parasomnia and insomnia with etiology other than tinnitus, were excluded from the sample.

In order to evaluate these criteria all patients were interviewed and examined by an otolaryngologist, an audiologist, and a psychologist. Sleep disorders were explored through a clinical interview with a physician specializing in sleep. The laboratory profile consisted of imaging studies (MRI or CT scan) and blood tests (blood lipids, thyroid hormones, glucose tests, urea, electrolytes and creatinine). Eleven subjects remained within the protocol, after one patient was excluded because stimulation was conducted during daytime and for short periods (average 1.5 hours daily usage).

Audiologic evaluation

Audiometric profiles were performed using impedanciometry, audiometry (exploring thresholds at 0.125, 0.25, 1, 2, 3, 4, 6, and 8 kHz), loudness discomfort levels (LDLs), speech audiometry and high frequency audiometry (8, 10, 12, 14 and 16 kHz; Table 1). Three types of otoacoustic emissions (OAEs) were measured: distortion product otoacoustic emissions (DPOAEs), transient evoked otoacoustic emissions (TEOAEs), and spontaneous otoacoustic emissions (SOAEs). DPOAEs were measured using three pairs of pure tones per octave in the range of 1–6 kHz. TEOAEs were studied with a broadband click in the range of 1–5 kHz.

Tinnitus profile

Tinnitus onset varied from 6 months to 28 years. In eight cases tinnitus was binaural and in three cases it was monaural. The spectral characteristics of the perceived sound were a combination of bandpass noise and pure tones in three patients; a combination of pure tones was referred by seven patients, and a noise band alone by one.

Psychological evaluation

Evaluation by a psychologist was performed at the beginning, in the middle (week 6), and at the end of the treatment (week 12). In each interview, patients were specifically evaluated for anxiety and depression. The impact of tinnitus on quality of life was assessed through three questionnaires: THI, TRQ, and TFI. The questionnaires were given to the patient prior to each interview, and the subjects were instructed to answer them alone. A VAS regarding tinnitus annoyance was also performed at each interview.

Sleep evaluation

Sleep quality was evaluated clinically in each interview. Subjective perception about time to sleep onset, maintenance of sleep, and early waking were explored. The repercussion on wakefulness, e.g. loss of memory, irritability, and somnolence were also evaluated. Tinnitus impact on sleep quality was evaluated through the TFI sleep subscale test.

Tinnitus characterization and sound stimulation

Taking into account that most tinnitus reported by patients was classified as complex sounds, i.e. combinations of pure tones, harmonics of the pure tones, white noise, and band noises (Henry, 2004), we designed software with the specific aim of matching the patients' perception by a highly customized sound. This software was loaded onto the physician's device (iPad). Separate software, which was capable of reproducing the customized sound, was loaded onto the patients' devices (iPod Touch). These devices allowed patients to set the intensity of sound stimulation every night and store sound-intensity data daily. These two programs—one running on the physician's iPad and the other on the patients' iPods—were designed to be able to communicate via WiFi, sharing data of intensity evolution and daily time of stimulation. Using this capability, information stored on the patient's iPod could be downloaded to the physician's iPad during each appointment and displayed graphically. Customized in-ear ear buds were created for each patient. Solid soft-gel medical grade silicon molds were made based on impressions taken from the ear canals. The molds were manufactured to achieve maximum occlusion, in order to avoid air leaks between the molds and the walls of the ear canal. They were also designed to not protrude from the ear's pinna. The latter two features were important to prevent the customized sound from being heard by surrounding people and to enable the patient to comfortably lay his/her ears on the pillow while sleeping. The occlusive molds did not move once they were located in the ear canal, staying in place during sleep, and thus ensuring a fixed distance between the source of sound and the eardrum. This point was fundamental for

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Table 1. Audiologic evaluation of the eleven patients.

Patient (gender, age)	*Tinnitus side and evolution (years)*	*Acuph. (dB HTL)*	*Sound match (dB SPL)*	*TLA (dB HTL)*	*Logo SRT (dB HTL)*	*HFA binaural thresholds at 10, 12, 14, and 16 kHz (dB SPL)*
TL f, 32	RL, 20	6 kHz 60 dB	3678 + 6678 Hz R,L = 54.1 dB	R,L: Normal	R, L: 5 dB	R: 40, 65, 50, 50. L: 40, 45, 45, 45.
EC f, 32	R, 1	4 kHz 40 dB	NBN 3560 Hz R = 44.1 dB	R,L: Normal	R, L: 10 dB	R: 40, 60, 75, 95. L: 30, 35, 40, 65.
GB f, 39	RL, 2	8 kHz 45 dB	7348 +NBN 7348 Hz R=54.1, L = 55.1 dB	R: Normal L:↓5–10 dB (0.5–2 kHz), ↓25 dB (6 kHz), ↓15 dB (8 kHz).	R, L: 20 dB	R: 60, 85, 95, 110. L: 60, 80, 85, 110.
WF m, 42	RL, 0.5	4 kHz 40 dB	4900 + 9800 Hz R,L = 43 dB	R,L:↓5–10 dB (2–4 kHz), ↓25 dB (6–8 kHz).	R, L: 10 dB	R: 75, 85, 90, 95. L: 85, 90, 90, 110.
MB f, 64	L, 3	NBN 4 kHz 45dB	4626 + 4526+4426 + 4326 Hz L = 60.5 dB	R:↓20 dB (4 kHz), ↓45 dB (6 KHz), ↓40 dB (8 KHz). L:↓20 dB (3 kHz), ↓35 dB (4 kHz), ↓50 dB (6–8 kHz).	R, L: 15 dB	R: 95, 105, 105, NR. L: 90, 105, 105, NR.
SO f, 60	RL, 4	8 kHz 45 dB	11444 + 10444+9400 + 9200 Hz R,L = 69.1 dB	R: Normal L:↓35 dB (3 kHz), ↓15 dB (4–6 kHz).	R, L: 25 dB	R: 60, 70, 95, NR. L: 65, 80, 95, 110.
LG f, 55	RL, 1	4 kHz 65 dB	6099 + 6200+6500 Hz R = 56.9, L = 63 dB	R:↓20 dB (3–6–8 kHz) L:↓15 dB (3 kHz), ↓30 dB (4 kHz), ↓20 dB (6 kHz), ↓35 dB (8 kHz).	R, L: 10 dB	R: 60, 105, NR, NR. L: 95, 110, NR, NR.
FC m, 58	RL, 12	NBN 8 kHz 65 dB	8000+ NBN10759 Hz R,L = 67.4 dB	R:↓25 dB (4 kHz), ↓55 dB (6 kHz), ↓65 dB (8 kHz). L:↓15 dB (4 kHz), ↓35 dB (6 kHz), ↓55 dB (8 kHz).	R, L: 10 dB	R: 105, 110, 105, 105. L: 95, 110, 105, 105.
MA m, 21	L, 3	4 kHz 65 dB	7561 + 15122 Hz L = 46.1 dB	R: Normal L:↓40 dB (4 kHz), ↓65 dB (6 kHz), ↓60 dB (8 kHz).	R, L: 5 dB	R: 45, 40, 50, 60. L: 95, 85, 85, 95.
MR M, 54	RL, 5	NBN 50 dB	9500 + 9000+10500 + 11- 00 Hz+ NBN 13317 Hz R,L = 67.6	R:↓15 dB (3 kHz), ↓50 dB (6 kHz), ↓15 dB (8 kHz). L:↓15 dB (3 kHz), ↓20 dB (2 kHz), ↓45 dB (6 kHz), ↓40 dB (8 kHz).	R: 20 dB L: 15 dB	R: 60, 90, 110, NR. L: 70, 105, 110, NR.
EP m, 32	RL, 2	4 kHz 55 dB	6601 + 6801 Hz R = 59.9 L = 65.9 dB	R:↓15 dB (4 kHz), ↓35 dB (6 kHz), ↓45 dB (8 kHz). L:↓15 dB (1–2 kHz), ↓35 dB (3–4 kHz), ↓55 dB (6–8 kHz).	R,L: 30 dB	R: 60, 75, 85, 95. L: 70, 75, 85, 100.

Acuph = acuphenometry; TLA = tonal liminal audiometry; Logo = logoaudiometry; SRT = speech recognition threshold; HFA = high frequency audiometry; R = right ear; L = left ear: NBN = narrowband noise: NR = no response

achieving stable and calibrated sound pressure in the ear canal. The molds were carved inside to allow for the electronic parts (Etymotic ER4 series drivers, impedance 20 ohms@ 1 kHz, sensitivity 103.5 dB SPL for 0.1V @ 1 kHz) to be mounted. A supple tour grade cable (52 inches long with silver clear jacket) was used to plug the ear buds to the iPod. Once completed, the system's output was calibrated using an artificial ear (Ear Simulator 43AC, GRAS sound and vibration), a microphone (Bruel & Kjaer type 2250), and a sound calibration system (Bruel & Kjaer type 4231 @ 1 kHz, 94 dB SPL). The response curve of all the customized ear buds used in this study was characterized and a mean response curve was derived. The frequency response curve obtained covered the range

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0.125–16 kHz and on average, the power difference between any earphone and the mean response curve was less than 3 dB SPL.

Tinnitus perception match

Each patient went through a process in which the physician created a custom combination of sounds that matched their tinnitus spectral and intensity characteristics. The previously described software and calibrated sound system provided the capability of presenting the patient five different types of sounds: pure tones, bandpass noise, a 'cricket' sound, white noise, and pink noise. For the pure tones, the frequency could be adjusted in the range 0.125 to 16 kHz. For the bandpass noise, the center frequency could be adjusted in the same range and the Q factor could be set to determine the bandwidth. The cricket sound was synthesized by defining a center frequency and two pairs of adjacent pure tones, one pair with higher and one pair with lower pitch. The center frequency could be set in the above-cited range and the frequencies of the adjacent tones were automatically set in relation to the center frequency. For the five types of sound, intensity could be adjusted in the range 0–85 dB SPL. The sounds could be presented separately or combined in order to match the patient's perceived sound. When sounds were combined, the system output was calibrated to calculate the overall SPL output. The sound match achieved through this procedure was required to be as similar as possible to the patient's tinnitus, in order to get better results in the treatment and more accurate intensity follow-up measurements.

Reliability and validity of the tinnitus sound match

Evaluation of the sound match accuracy was performed a week after the customized sound was first created. Patients' feedback was requested on the capacity of the sound to mask their tinnitus. The sound was changed if it did not achieve that goal. Once masking was verified, VAS on the similarity to the tinnitus was conducted in order to obtain a customized sound that not only masked the tinnitus but also was as similar as possible to the patient's perception. This latter point was important because the more similar the sound match was to the patient's perception, the less intensity was required to mask it and therefore the more accurate the intensity measurement was and the intensity follow-up. In the VAS the patient was asked to rank the matching between 0 (totally different from tinnitus) and 10 (exactly the same as the perceived tinnitus). A sound match that scored over 6 in the VAS scale and covered the patient's perception was accepted to start the treatment. If the sound match did not fulfill these conditions, the procedure was repeated, modifying the sound until it did. The average VAS score for tinnitus match in this study was 8.3, while the average VAS score for acuphenometry was 4.1. The difference observed in these scores was statistically significant (Wilcoxon test $p < 0.05$).

Treatment protocol

Tinnitus intensity was measured before going to sleep each night for seven days, as described below. Patients were instructed not to perform the stimulation during this period in order to have a 'control week' of tinnitus evolution without sound stimulation. Once the control was established, they were treated with customized sound stimulation during sleep, every night for three months. An additional three months of follow up were performed. During the follow up periods, patients were permitted to use the stimulation at night on a self-determined, as needed basis. Patients were instructed to stimulate every night and to set the intensity of stimulation at the lowest intensity above their perceived sound. Data regarding intensity of the stimulation in dB SPL and daily usage was stored on each device. Based on these data, an intensity follow up was performed providing information about the evolution of the treatment. Every fifteen days appointments were set to evaluate stimulation, sleep, and psychological performance. In each one of these appointments, data from the devices were downloaded, stored and displayed both graphically and as a log on the physician's iPad. If the patient reported a change in the spectral characteristics of their tinnitus, the customized sound was adapted in order to match that change.

Data analysis

Tinnitus intensity

The use of a stimulating sound that matches tinnitus, and the calibrated system with fixed ear buds in the ear canals, allowed us to obtain accurate information on the evolution of tinnitus intensity. This gave us the opportunity to get more precise data in dB SPL, in contrast to intensity information obtained in our previous study, which was quantified by steps of sound volume of the stimulation device (Pedemonte et al, 2010). Daily intensity averages of the eleven patients were obtained for the 'control week.' Statistical significance was analysed using a repeated measurements ANOVA. For the three months of stimulation during sleep, weekly averages of daily intensity were calculated for each patient. A tinnitus overall weekly intensity value was obtained by averaging the eleven patients' individual averages for each week of treatment. Statistical significance was obtained using the Wilcoxon test.

Psychometric tests

The Wilcoxon test was performed in order to assess statistical significance of the evolution of the questionnaires (THI, TRQ, and TFI).

This research has been approved by the Ethical Committee of the Faculty of Medicine CLAEH University, according to the International Ethic Guidelines for Human Research. Patients were informed and signed a letter of consent.

Results

Eleven patients suffering from subjective idiopathic tinnitus were included in this protocol. Audiological evaluations showed no hearing loss in four patients and mild neurosensory hearing loss within the 3–8 kHz range in seven of them, binaurally symmetric for two patients and asymmetric for the remaining five. In those patients with asymmetric hearing loss, the tinnitus was only present or was louder in the most affected side. A mean audiogram of the participants is shown in Figure 1, panel A. The audiological profile in the high frequencies (10, 12, 14, and 16 kHz) is displayed in Table 1. The logo-audiometry showed speech recognition thresholds (SRT) between 5 and 30 dB HTL with a mean of 14.1 dB HTL. No patient presented recruitment. LDLs were normal in eight out of eleven patients. Regarding the OAE evaluation, DPOAEs in at least one frequency were observed in every patient. Different degrees of intensity decrement or absence of response in the range of 2–6 kHz were observed in nine patients. Only two patients (TL and EC) presented consistent responses in the whole range studied.

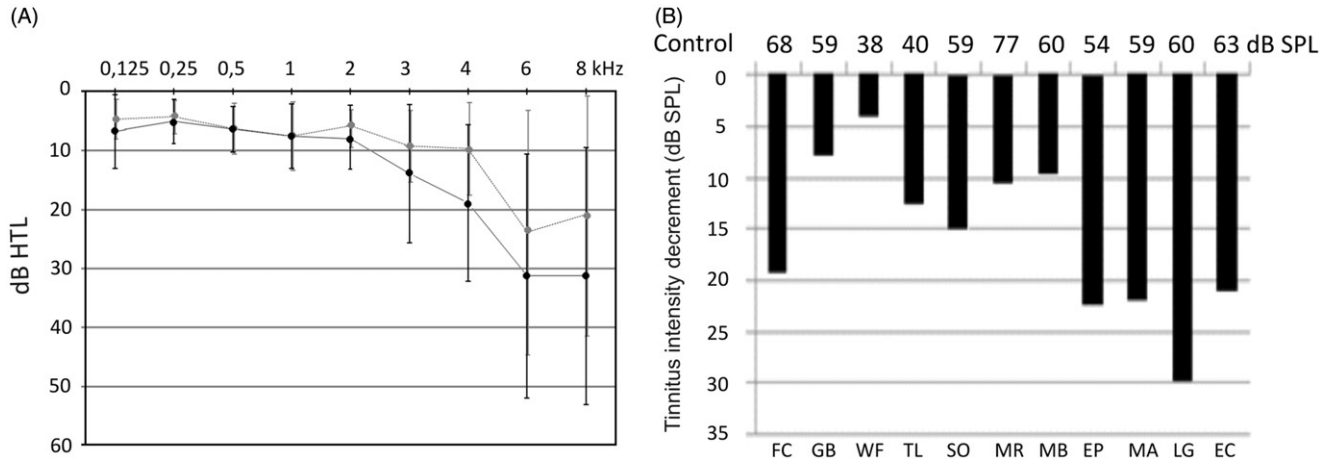

Figure 1. (A) Mean audiogram of the participants. For each frequency a mean of liminal thresholds and their standard deviation is plotted. (B) Decrease of tinnitus intensity. Bars show intensity reduction for each patient (in dB). Zero corresponds to the measurement of tinnitus intensity before treatment (average of seven days); the range of decrease was between 3.9 to 29.8 dB, taking into account the values of the twelfth week of treatment. At the top (Control), initial levels of tinnitus intensity in each patient are shown.

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TEOAEs were present in nine out of eleven patients (not present in MA and SO). Seven patients presented TEOAEs with different degrees of intensity decrement or absence of response in the range 3–5 kHz. Only two subjects (TL and EC) showed responses in the whole range studied. SOAEs were observed only in two patients (TL and EC).

The patients included in this study were stimulated nightly for three months with customized sound. Three different tools were used in order to analyse the effectiveness of the treatment: (1) intensity reduction of tinnitus measured in dB; (2) psychological evaluation of tinnitus through THI, TRQ, and TFI tests; and (3) a VAS for tinnitus annoyance.

Intensity reduction

The eleven patients studied showed a decrease of the tinnitus intensity that varied from a maximum of 29.8 dB to a minimum of 3.9 dB (Figure 1, panel B). Each patient showed a statistically significant decrease in tinnitus intensity, comparing seven values collected in the control week with seven values in week 12 ($p < 0.05$). Statistical significance was evaluated using the Wilcoxon signed-rank test (nonparametric, paired samples).

The average tinnitus intensity over all 11 patients showed no statistically significant difference during the seven days before the beginning of stimulation ('control week', Figure 2, panel A). The intensity values obtained from the 'control week' were averaged to obtain the control level prior to starting treatment. During the three-month period of stimulation, a statistically significant intensity reduction of an average 14.1 dB ($p < 0.001$) was observed between the 'control' (mean 58 dB SPL), and week twelve of the study (mean 43.9 dB SPL, Figure 2, panel B).

During the study, no patients experienced an increase in the intensity of their tinnitus, although in none of them the tinnitus completely disappeared. The degree of improvement was not associated with the sound characteristics of tinnitus or the intensity during the 'control' week. Also, no significant correlation was observed between the effect of treatment and time evolution of tinnitus; the two patients with most longstanding tinnitus (TL, FC) showed intensity reductions close to the average of the sample.

The weekly analysis showed a progressive decrease in the intensity of the tinnitus (Figure 2, panel B). The greatest intensity reduction happened in the first week of stimulation, with a mean decrease of 8.5 dB between 'control' and week one ($p < 0.001$). Further intensity reduction of 5.6 dB happened between week one (mean 49.5 dB SPL) and week twelve (mean 43.9 dB SPL), however, this reduction was not statistically significant ($p = 0.054$). After three months of daily stimulation all patients but one, (MR), reported being unaware of their tinnitus for long periods during the day. All patients stated that they continued to hear their tinnitus in quiet indoor environments at night. Three patients (MA, LG, and EP) referred that they stopped hearing their tinnitus for periods between one and three days, even before going to sleep. Those patients reached tinnitus intensity levels that ranked between 30 and 32 dB SPL.

The daily average stimulation time for this study was 6.2 hours per night.

THREE-MONTH FOLLOW UP

Three additional months of follow up were performed. During this period, stimulating every night was not required and patients were advised to continue nightly stimulation on a self-determined, 'as needed', basis. One patient (MR) left the treatment after the first three-month period. Of the ten patients who were evaluated at week twenty-four, the average intensity measured was 41 dB SPL, which was a statistically significant reduction compared with the first week ($p < 0.01$) but not compared with week twelve.

Psychological evaluation of tinnitus

The results of the three psychometric tests performed showed statistically significant improvements. The biggest improvement was between the first and second round of tests (the first forty-five

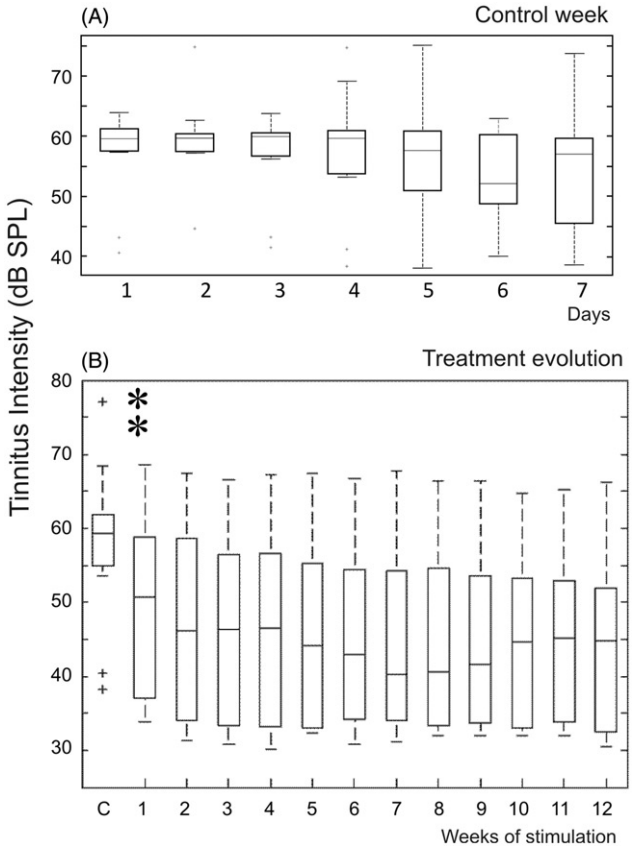

Figure 2. Evolution of tinnitus intensity through 12 weeks. (A) Box plot showing averages of tinnitus intensity measured during seven days without stimulation. Each box represents the daily average for eleven patients. No statistically significant changes were observed between the tinnitus intensity averages ($p = 0.09$, ANOVA). (B) Box plot showing the average weekly intensities for eleven patients during three months of stimulation during sleep. C is the Control considering the average across seven days of tinnitus intensity measurements prior to the beginning of stimulation. On average, tinnitus intensity decreased 14.1 dB between Control and week 12. These results are statistically significant (**, $p<0.001$) comparing values between Control versus the 1st week and Control versus the 12th week (Wilcoxon test).

days of treatment) with an average decrease of 27.3 for THI ($p<0.001$), 39.0 for TFI ($p<0.001$), and 24.7 for TRQ ($p<0.01$, Figure 3). During the third round of tests (at the end of the third month of treatment), the results still showed improvement in comparison to the second round, however, these changes were not statistically significant. The analysis of TFI showed statistically significant decreases between the first and second rounds for the intrusive, sense of control, sleep, relaxation, emotional, and quality of life subscales. Also, significant changes were observed between the first and third rounds of tests for all the subscales (Table 2), with especially relevant improvements of sleep and relaxation, which had reductions of 55.1 and 52.7, respectively. Sleep was also evaluated clinically in all patients in each interview, showing an improvement in their quality and quantity of sleep. Patients reported falling asleep faster, waking up fewer times during the night and/or experiencing longer sleep times.

Visual analog scale (VAS) for tinnitus annoyance

A VAS was used to determine and quantify the level of annoyance induced by the tinnitus. The VAS was performed before starting the treatment (Pre), in the sixth week (Middle) and twelfth week (Post). All the patients but one (MR), showed a reduction in their tinnitus annoyance. The average result of the scores was 6.53 for the pre-round of tests, and 3.88 and 2.55 for the middle and post-rounds, respectively. An overall improvement of 61% of the pre-treatment scores was observed. The difference between pre- and middle average scores was statistically significant (Wilcoxon: $p<0.001$).

Discussion

Our previous pilot study showed that sound stimulation during sleep is effective in reducing tinnitus intensity (Pedemonte et al, 2010). However, no data were available on either the precise amount of dB reduction or its impact on the patient's quality of life. In the present study, our aim was to establish whether there is a relationship between the decrease in intensity and improvement in the quality of life. The results showed a mean perceived-intensity reduction of 14.1 dB, followed by significant improvement in the scores of three psychometric tests and a VAS for tinnitus annoyance.

Intensity reduction

Each patient showed statistically significant decrements when control intensity values were compared with week 12 ($p<0.05$). The averages across the 11 patients showed a mean intensity reduction of 14.1 dB. Even taking into account that a great variability appeared in the weekly intensity averages, which may have been related to the small sample size, those results were significant ($p<0.001$). The 'physical correlate theory of sensory scaling' states that intensity half loudness is equal to half sound-pressure level (−6 dB SPL, Warren, 1973). According to this, the 14.1 dB reduction achieved correlates to a reduction of 80% of its original value. Assuming that a reduction of 10 dB decreases the level perception by half (Plack, 2005), the perceived tinnitus level displayed an average reduction of 62% compared to pre-treatment values.

All subjects decreased the intensity of tinnitus regardless of age, the evolution of the symptoms over time, and the audiological profile. This suggests that the treatment may be beneficial in a broad patient population. It is our assumption that the failure to find significant differences in the values of intensity reduction relative to these variables may be related to the small sample size of this study. Studies with larger sample sizes will be needed to demonstrate those differences.

Score improvement in psychometric tests

We executed three different tinnitus questionnaires and a VAS for tinnitus annoyance. In the THI, clinically significant improvement was defined in previous studies as a reduction of at least 20 points (Newman et al, 1998; Davis et al, 2007). Our results showed a mean decrease of 32 points and a 65% improvement over pre-treatment THI averages. Regarding the TRQ, previous studies set clinically significant improvements at values of 40% of pre-treatment (Hazell, 1999: McKinney et al, 1999). Our results showed a change from 39.9 pre-treatment to 8.9 post-treatment averages, meaning an average improvement of 78% of pre-treatment TRQ. With respect to the TFI, according to published data, a change in the score of 13

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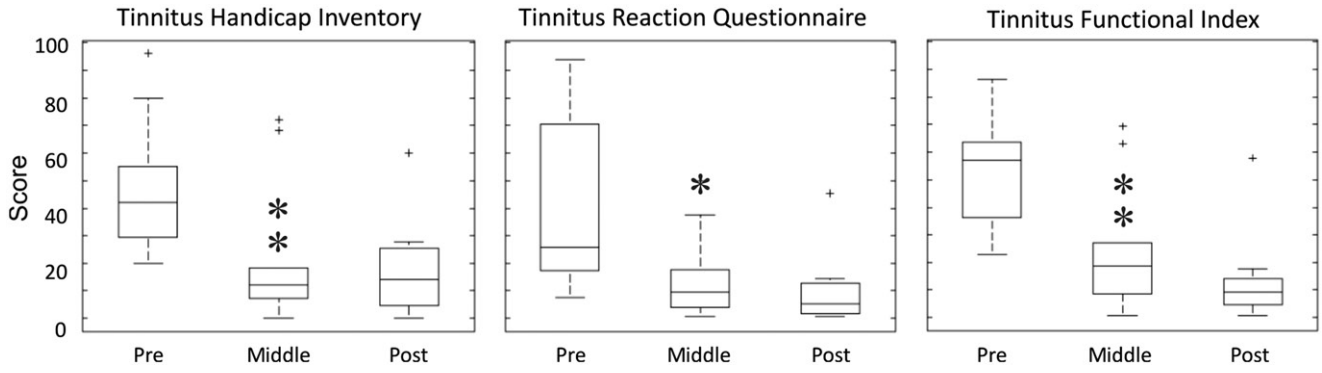

Figure 3. Psychometric evolution of patients. Psychometric assessment was conducted using three tests: Tinnitus handicap inventory, Tinnitus reaction questionnaire, and Tinnitus functional index. These were performed before starting treatment (Pre), and in the sixth week (Middle) and twelfth week (Post) after starting treatment. Statistically significant differences were found between (Pre) and (Middle) values, in all three tests (THI and TFI, $**$, $p < 0.001$; and TRQ $*$, $p < 0.01$, Wilcoxon test).

Table 2. Tinnitus functional index subscales were analysed separately; each number corresponds to the average of eleven patients. Asterisks identify statistically significant changes between Control versus Middle and Control versus Last test ($*$, $p < 0.05$; $**$, $p < 0.001$; Wilcoxon test).

Subscales	*Control*	*Middle test (6 weeks)*	*Last test (12th week)*
Intrusive (unpleasantness, intrusiveness, persistence)	51,4	33,2*	34,9*
Sense of control (reduced)	67,0	41,3*	30,8*
Cognitive (cognitive interference)	32,1	19,1	8,2*$*$
Sleep (sleep disturbance)	68,4	28,2*	13,3*
Auditory (auditory difficulties attributed to tinnitus)	29,8	11,3*	10,5*
Relaxation (interference with relaxation)	64,2	29,7*	11,5*$*$
Quality of life (reduced)	35,9	13,9*	5,1*
Emotional (emotional distress)	51,2	18,5*	12,5*

should be considered meaningful (Meikle et al, 2011). The mean decrease observed for TFI was 48 points, meaning a reduction of 77% of pre-treatment TFI scores. The TFI's subscale for sleep quality was particularly important for this study in order to assess the impact of treatment that is applied during sleep. Sleep has a direct impact on tinnitus (and vice versa) and if the treatment improves sleep quality, it may be more efficient in improving quality of life as a whole.

The results of the VAS for tinnitus annoyance observed (61% reduction of the pre-treatment values) are in harmony with previously published data, which correlates the VAS results with THI reduction outcome (Figueiredo et al, 2009).

Effectiveness of sound stimulation during sleep

We postulate that the treatment used in this study is effective due to: (1) the use of a highly customized sound stimulation, and (2) stimulation during sleep.

Customized sound stimulation

Currently there is wide consensus that tinnitus is mostly generated by a disruption of the input and that tinnitus pitch develops in correlation to the frequencies that are in deficit (Roberts et al, 2008; Schaette et al, 2010); moreover, the pitch is related to the slope edge frequency of the audiogram (König et al, 2006). Schaette et al (2010) suggest that acoustic stimulation treatments for tinnitus are most effective when tinnitus pitch is within the stimulated frequency range. It is our tenet that stimulating with the specific spectral and intensity characteristics of the perceived sound, may be an effective way of restoring the resulting deficits of auditory information that arise in the genesis of tinnitus. Using a sound that matches the patient's perception has additional advantages: (1) it has a relaxing effect, because during the stimulation the patient hears the sound coming from outside and stops hearing it in his head or ears; (2) it provides psychological relief since the patients realize that their tinnitus is reproducible and understandable by others; and (3) it also allows for the possibility of tracking how the intensity evolves through the course of treatment. Using a sound that matches tinnitus enables more accurate measurements of intensity. Marking their progress gives the patient psychological reinforcement and acts as a physician's tool for monitoring the treatment.

Other tinnitus treatments also use sounds that are related to the frequency ranges of the tinnitus. Phase shifting treatment uses a pure tone with a frequency similar to the tinnitus which is phase-shifted 180° to produce sound cancelling. Since only pure tones are used and most forms of tinnitus are complex, it is our tenet that this treatment would not be as effective for most patients. Statistically significant reductions of 23% in the VAS loudness scale and 13% in the Tinnitus Questionnaire were reported using this treatment (Vermeire et al, 2007). Some recent studies found that the treatment failed to demonstrate a significant effect and that no positive effect could be attributed to phase-shifting (Meeus et al, 2010; Heijneman et al, 2012). The Neuromonics tinnitus treatment provides an

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individually customized acoustic stimulus that is followed by structured counseling. The acoustic stimulus consists of music tracks that are spectrally modified according to each patient's individual audiometric profile in order to provide stronger stimulation at the frequencies where the audiogram shows lowered hearing thresholds (Wazen et al, 2011). Since those frequencies are strongly correlated with the spectral characteristics of the tinnitus (Schaette et al, 2010)—similar to what happens during our treatment—the tinnitus pitch is within the stimulated frequency range. Mean improvements in TRQ score of 66% were reported using the Neuromonics treatment (Davis et al, 2008).

We postulate that the more precisely the stimulating sound relates to the frequency profile of the tinnitus the better the outcome of the treatment. The fact that the stimulation in our protocol is closely matched to the frequencies of the tinnitus and no stimulation is provided in the rest of the audible range may constitute a stronger signal for attracting inhibition to the brain area generating tinnitus, and thus activating plastic changes. The values of intensity reduction and improvement in psychometric tests scores observed in the present study support this tenet, although further studies with larger sample sizes will be needed to confirm it.

Stimulation during sleep

It is well accepted that sleep has an effect on learning and memory (Velluti, 2008; Velluti et al, 2010; Velluti & Pedemonte, 2012). As discussed in our previous paper (Pedemonte et al, 2010), sound stimulation during sleep is beneficial because it affords a maximum amount of available treatment hours during a time when fewer additional sensory inputs occur. Furthermore, patients are not aware of the stimulation and there is no interference with daytime activities. These advantages may make a significant difference compared to other treatments that use customized acoustic stimulation during daytime (i.e. Neuromonics, Phase Out, Notched music, S-tones) for shorter periods.

The sleep subscale of the TFI improved with this treatment, perhaps as a consequence of the decrease in tinnitus intensity. However, further studies may be required to demonstrate the correlation between tinnitus intensity variation and sleep quality.

Conclusions

These results demonstrate that the reduction in intensity of tinnitus achieved through this treatment is directly related to an overall improvement in the patients' quality of life. The more accurate quantification of tinnitus intensity uncovered what appears to be a correlation between changes in intensity and changes of scores of psychometric tests. This idea is supported by our results, which demonstrated a reduction of loudness perception of the tinnitus, THI, TRQ, TFI, and VAS of 62%, 65%, 78%, and 61%, respectively. Studies with larger sample sizes will be needed to reinforce this conclusion. The effectiveness of the protocol used in this study could be explained by the use of a combination of a highly customized acoustic stimulus, similar to the patient's perceived sound, and stimulation during sleep.

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