Los doctores Daniel Drexler y Marisa Pedemonte, junto a los ingenieros Andrés Bianco y Darío Geissinger, desarrollaron en los últimos 17 años un sistema de estimulación acústica durante el sueño para tratar a las personas que sufren de tinnitus.

Tinnitus es el término médico para definir un síntoma que consiste en "escuchar" ruidos cuando no hay una fuente sonora externa que los origine. Comúnmente se le conoce como acúfeno o zumbido. El tinnitus es un problema de salud a nivel mundial para el que no existe cura. Se calcula que afecta entre un 15 y un 17% de la población. Es una patología que puede volverse insoportable y afecta especialmente a los músicos.

Daniel Drexler es músico, médico y magister en neurociencias. Ese perfil médico se combinó con su costado musical para originar la idea en la que se basa el nuevo tratamiento. La doctora y Phd en ciencias Marisa Pedemonte, con quién Drexler había trabajado en el Laboratorio de Neurociencias de la Facultad de Medicina, se sumó al proyecto en sus estadios iniciales aportando sus conocimientos en fisiología de la audición durante el sueño. De esta conjunción entre clínica y ciencia básica y entre música e ingeniería biomédica, surgió el "Tratamiento para el Tinnitus con Estimulación Acústica durante el Sueño".

Para desarrollar el tratamiento y el dispositivo biomédico asociado al mismo, se sumaron al grupo los ingenieros Andrés Bianco y Darío Geisinger, fundándose la Start Up Uruguaya "Otoharmonics S.A.". En 2008 se logra terminar el primer prototipo de software y hardware, llamado "Levo", con fondos de la Agencia Nacional de Investigación e Innovación del Uruguay (ANII) y la contribución del centro médico estadounidense Cedars Sinai. Entre 2009 y 2012 se realizan en Montevideo tres ensayos básico-clínicos obteniéndose un promedio de reducción de la intensidad del tinnitius del 62% en comparación con los valores pre-tratamiento. Estos auspiciosos resultados despiertan el interés por el proyecto en USA, lo que lleva a la formación en Portland, Oregon, de la corporación "Otoharmonics Corp." la que adquiere el “know-how” y el software y hardware desarrollado en Uruguay y absorbe a la original “Otoharmonics S.A.”.

En 2015 Otoharmonics Corp. adquiere en su totalidad las patentes y los derechos de comercialización de "Levo", iniciando la comercialización en el mercado de USA, Canadá y UK. En la actualidad, "Levo" cuenta con la habilitación de la Comunidad Económica Europea (marca CE) y la Food and Drugs Administration de USA (FDA). Asimismo, dos patentes fueron aprobadas en 2016 por la Agencia de Patentes de USA (USPTO). Ambas patentes han sido también levantadas en la CEE, México, China, Canadá, India, Corea del Sur y Australia.

En los últimos tres años el tratamiento ha sido reafirmado en ensayos clínicos de otras partes del mundo, destacándose el Trial clínico desarrollado por el Dr. James Henry a fines del año pasado en el prestigioso Hospital de Veteranos de Portland, centro de referencia para el Tinnitus a nivel mundial. En este Trial, “Levo” fue comparado con otros dispositivos utilizados en la actualidad para el tratamiento del tinnitus, obteniendo resultados significativamente mejores.

En este momento la estimulación sonora durante el sueño está siendo utilizada para tratar pacientes en Estados Unidos, Canadá y Gran Bretaña. Asimismo, está en curso la habilitación para su uso en otros países.

El pasado 13 de junio de 2017, el dispositivo biomédico desarrollado casi en su totalidad en Uruguay, fue distinguido con la medalla de oro en la categoría “Digital Health Products and Mobile medical Apps” de los “19th Annual Medical Design Excellence Awards” en Nueva York, Estados Unidos. Este premio es el máximo galardón de la industria biomédica en USA.
El último trimestre de 2017 se publicó un paper en la American Journal of Audiology con los resultados de un ensayo clínico realizado en el VA Hospital de Portland, Oregon, en el que se compara positivamente el resultado obtenido en el tratamiento de

pacientes con Levo con los obtenidos con otro dispositivo comúnmente usado en clínica en USA.

Estimulación Acústica durante el Sueño

Este nuevo protocolo de tratamiento consiste en la estimulación con sonido que mimetiza las características del tinnitus. El sonido se crea de manera individualizada buscando que sus características de intensidad y espectro de frecuencias reproduzcan lo que el paciente escucha. Una vez generado el sonido, se lo carga en dispositivos portátiles (iPod Touch) y mediante auriculares innear se lo aplica durante el sueño.

Este tratamiento produce una disminución sostenida de la intensidad del tinnitus mejorando sustancialmente la calidad de vida de los pacientes.

“Lo que hacemos es devolverle al paciente el mismo sonido que tiene en la cabeza, para que el propio cerebro inhiba el flujo de información en esas frecuencias. La idea que hay detrás del tratamiento es aprovechar la maravillosa capacidad que tiene nuestro cerebro de adaptarse a nuevas situaciones a través de la neuroplasticidad. Resumiendo; le damos pautas acústicas al cerebro para que corrija el desequilibrio que él mismo generó”, explica Drexler.

International Tinnitus Journal. 2010;16(1):37-43.

Tinnitus treatment with sound stimulation during sleep

Pedemonte M.,
Drexler D.,
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Geisinger D.,
Bianco A.,
Pol-Fernandes D.,
Bernhardt V.

Abstract

A new strategy for idiopathic subjective tinnitus treatment – sound stimulation during sleep – has been applied. It was based on the knowledgement that the auditory system also works during sleep, processing the incoming information. Eleven patients were stimulated every night during 6 months. The stimulus was a sound that mimetized the tinnitus and was fixed at the same tinnitus intensity, applied through an iPod. All patients decreased their tinnitus intensity in the first month of treatment (statistically significant), most of them in the first week. Tinnitus intensity continued decreasing in the following weeks; three patients presented periods of total silence.

Keywords: Tinnitus, Treatment, Sleep.

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Brief summaries were presented in the following meetings:
2nd Tinnitus Research Initiative Meeting, Principality of Monaco, 2007.
World Federation of Sleep Medicine Sleep Research Societies, Cairns, Australia, 2007
III XXX Congress of Association for Research in Otolaryngology, Phoenix, Arizona, USA, 2008
World Association of Sleep Medicine Congress, Sao Paulo, Brazil, 2009.

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Sleep Science

The Impact of Sound on Electroencephalographic Waves during Sleep in Patients Suffering from Tinnitus

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ABSTRACT

Based on the knowledge that sensory processing continues during sleep and that a relationship exists between sleep and learning, a new strategy for treatment of idiopathic subjective tinnitus, consisted of customized sound stimulation presented during sleep, was tested. It has been previously shown that this treatment induces a sustained decrease in tinnitus intensity; however, its effect on brain activity has not yet been studied. In this work, we compared the impact of sound stimulation in tinnitus patients in the different sleep stages.

Ten patients with idiopathic tinnitus were treated with sound stimulation mimicking tinnitus during sleep. Power spectra and intra- and inter-hemispheric coherence of electroencephalographic waves from frontal and temporal electrodes were measured with and without sound stimulation for each sleep stage (stages N2 with sleep spindles; N3 with slow wave sleep and REM sleep with Rapid Eye Movements).

The main results found were that the largest number of changes, considering both the power spectrum and wave's coherence, occurred in stages N2 and N3. The delta and theta bands were the most changed, with important changes also in coherence of spindles during N2. All changes were more frequent in temporal areas. The differences between the two hemispheres do not depend, at least exclusively, on the side where the tinnitus is perceived and, hence, of the stimulated side. These results demonstrate that sound stimulation during sleep in tinnitus patients' influences brain activity and open an avenue for investigating the mechanism underlying tinnitus and its treatment.

1. Introduction

While all sensory processing persists during sleep, the auditory input is particularly relevant for continuously monitoring the environment [1,2].

Several treatment strategies of tinnitus are based on sound stimulation and evidence indicates that they are more effective if sound mimics the tinnitus [3]. All these protocols conduct sound stimulation during the day, while patients are awake. Based on the knowledge that auditory processing continues during sleep [2] and that a relationship between learning and memory and sleep stages has been established, our group has embarked a new strategy for the treatment of idiopathic subjective tinnitus. A protocol of customized

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Cochlear microphonic changes after noise exposure and gentamicin administration during sleep and waking

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Abstract

These experiments were designed to investigate the effect of noise, sleep, and gentamicin on the cochlear microphonic (CM) of the guinea pigs. Are the changes observed due to intrinsic cochlear phenomena or to efferent system actions? To answer this question, noise exposure together with efferent system blockade by gentamicin administration was performed. In the normal (non-treated) animal, noise exposure decreased both variability and amplitude of the tone evoked CM in about the first 10 min while the physiological modulation of slow wave sleep increasing the CM is not present. Following administration of gentamicin, noise no longer affect the CM in about the first 10 min, although it produces amplitude and variability increments. The influence of slow wave sleep on the CM is not altered. Thus, gentamicin does not block the CM sleep/wakefulness related shifts. The data were discussed in terms of the influence of gentamicin on the olivo-cochlear bundle. It was hypothesized that the effects of noise on the CM is a result of both peripheral and central influences.

Keywords: Cochlear microphonic; Sleep wakefulness; Gentamicin white noise exposure; Efferent system; Olivo-cochlear bundle

1. Introduction

The auditory system is a neuronal network with profuse interconnections at various levels. This anatomical structure underlies the complex processing exhibited by the auditory system which performs many communication related skills. In addition, the auditory system has a set of neurons whose axons extend from the auditory cortex to the periphery, constituting the efferent, descending system in parallel to the classical ascending pathway (Desmedt, 1975; Velluti and Pedemonte, 1986; Huffman and Henson, 1990; Spangler and Warr, 1991; Warr, 1992; Guinan, 1996; Xiao and Suga, 2002; Khalfa et al., 2001). After establishing multiple synaptic contacts along their course, these fibers terminate on the cells of origin of the olivo-cochlear bundle which project to the cochlear nucleus and the cochlea, establishing synapses on outer/inner hair cells and on primary fibers.

The efferent system has been considered a modulator of the auditory input after the classical work by Galambos (1956) using electrical stimulation of the olivo-cochlear bundle at the floor of the 4th ventricle, in a rather artificial condition. New evidence includes cochlear potential analysis in quasi-physiological experimental conditions that revealed: (1) During acoustic habituation – with middle ear ossicles removed and sound directly applied to the bulla superior recessus- the averaged cochlear microphonic (CM) and auditory nerve compound action potential (cAP) showed a significant and parallel amplitude decrease in freely moving guinea pigs. This was associated with an instantaneous amplitude recovery – dishabituation – in response, e.g., to simultaneous olfactory stimulation (Buno et al., 1966). (2) When a cat's attention was focused on a visual discrimination task, the evoked potentials of the auditory cortex, the cochlear nucleus and the auditory nerve

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Abbreviations: CM, cochlear microphonic; CNS, central nervous system; cAP, compound action potential; OAE, otoacoustic emission; DPOAE, distortion product otoacoustic emission; EMG, electromyogram; ECoG, electrocorticogram; SWS, slow wave sleep

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

Daniel Drexler, Matías López-Paullier, Silvana Rodio, Manuela González, Darío Geisinger & Marisa Pedemonte

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Randomized Controlled Trial of a Novel Device for Tinnitus Sound Therapy During Sleep

Sarah M. Theodoroff, Garnett P. McMillan, Tara L. Zaugg, Megan Cheslock, Chan Roberts, and James A. Henry

+ Author Affiliations & Notes

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Purpose The aim of this study was to determine if a customized stimulus from the Otoharmonics Levo System reduces tinnitus perceptions and reactions for people with bothersome tinnitus.

Method Sixty participants were randomized to 1 of 3 groups that used sound therapy devices during sleep that differed in their acoustic stimulus: (a) tinnitus-matched (TM), (b) noise stimulus (NS), and (c) bedside sound generator (BSG). Outcome measures were the Tinnitus Functional Index (TFI), numeric rating scale of tinnitus

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Drexler et al.

(10) **Patent No.: US 9,282,917 B2**
(45) **Date of Patent: Mar. 15, 2016**

(54) **SYSTEMS AND METHODS FOR A TINNITUS THERAPY**

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(72) Inventors: **Daniel Drexler**, Montevideo (UY); **Michael Baker**, Portland, OR (US); **Marisa Pedemonte Bemvenuto**, Montevideo (UY); **Dario Geisinger Yasky**, Givat Shmuel (IL); **Andres Bianco de Olea**, Lomas de Solymar (UY)

(73) Assignee: **Otoharmonics Corporation**, Portland, OR (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1 day.

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(51) **Int. Cl.**

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H03G 3/00	(2006.01)
H04R 25/00	(2006.01)
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(58) **Field of Classification Search**
CPC H04R 25/75
See application file for complete search history.

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Primary Examiner — Curtis Kuntz
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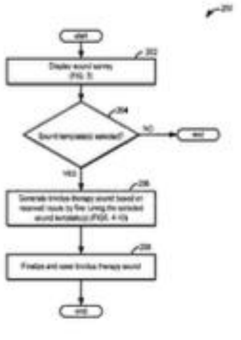
(57) **ABSTRACT**

The treatment of tinnitus may include a tinnitus therapy including generating a tinnitus therapy sound that is similar to a patient's perceived tinnitus sound. In one example, a method for generating a tinnitus adjusted sound may include presenting a plurality of different sound templates to a user from a series of tinnitus therapy sound templates, receiving a selection by the user of one or more of the templates, receiving an adjustment to one or more of the selected templates, and generating a therapy sound based on the adjusted selections.

14 Claims, 22 Drawing Sheets



US009301714B2

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Baker et al.

(10) Patent No.: US 9,301,714 B2
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(54) **SYSTEMS AND METHODS FOR TRACKING AND PRESENTING TINNITUS THERAPY DATA**

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(73) Assignee: **Otoharmonics Corporation**, Portland, OR (US)

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(58) **Field of Classification Search**

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Primary Examiner — Mark Blouin

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(57) **ABSTRACT**

The treatment of tinnitus may include a tinnitus therapy including generating a tinnitus therapy sound that is similar to a patient's perceived tinnitus sound. In one example, a method for tinnitus therapy may include tracking a tinnitus therapy over a duration, the tinnitus therapy including a tinnitus therapy sound matching a patient's perceived tinnitus played over the duration and presenting each of a volume evolution of the tinnitus therapy sound and usage data of the tinnitus therapy over the duration.

20 Claims, 21 Drawing Sheets