

Effectiveness of Combined Counseling and Low-Level Laser Stimulation in the Treatment of Disturbing Chronic Tinnitus

Domenico Cuda and Antonio De Caria

Department of Otolaryngology, Guglielmo da Saliceto Hospital, Piacenza, Italy

Abstract: We recruited 46 adult patients affected by disturbing tinnitus lasting for at least 3 years. All were treated with a combined counseling protocol constituting hypnotherapeutic and muscle relaxation techniques. We randomly assigned 26 patients to the group receiving low-level laser stimulation treatment and 20 to the placebo group. The laser power was 5 mV and the wavelength 650 nm. The irradiation lasted 20 minutes daily for 3 months. The Tinnitus Handicap Inventory (THI) questionnaire was submitted at the beginning and at the end of treatment. The THI scores improved in the entire sample after treatment but more significantly in the group receiving low-level laser stimulation. From the point of view of clinical classification, approximately 61% of irradiated patients had tinnitus severity decreased by one class, in comparison to 35% of the placebo group.

Key Words: ericksonian hypnosis; soft laser therapy; TinniTool; tinnitus

Tinnitus is the perception of a “phantom” sound that does not actually exist [1]. It often is a disabling symptom of different disorders affecting the auditory system, and it can be associated with a wide range of pathological conditions. Tinnitus must be distinguished from real auditory hallucination, which is a symptom of psychiatric or neurological disorders.

The patient’s ability to tolerate tinnitus varies; those patients who seek treatment have not been able to develop the habit of living with the symptom. The general belief is that most of the people who seek treatment for “auditory buzzing” benefit simply from clinical examination and from the doctor’s reassurance about the benign nature of the symptom. Yet, for those needing further treatment, several different therapeutic approaches are available today, and they are usually multidisciplinary. These are specific treatments, aimed to reduce the negative effects of the disorder; however, treatment leads in only rare cases to complete disappearance of tinnitus.

This study was carried out with the objective of assessing in a prospective and controlled way the effectiveness of two different therapeutic strategies for which preliminary

effectiveness tests gave conflicting results. The combined strategies are counseling and low-level laser stimulation.

MATERIALS AND METHODS

Recruitment Criteria

We studied 46 adult patients (age range, 28–83 years; mean, 56.4 years; standard deviation [SD], 13.7 years) who consecutively sought treatment at the tinnitus clinic of the Guglielmo da Saliceto Hospital in Piacenza. Twenty-seven of the patients were male, and 19 were female. The recruitment criterion was that patients had to be adults suffering for at least 3 months with disturbing nonintermittent subjective tinnitus. Patients with frank preexisting psychiatric pathology (psychosis, major depression, etc.), those with “retrocochlear” pathology (acoustic neurinoma, etc.), and those involving medicolegal disputes related to tinnitus were excluded. Recruited patients received detailed information about the objectives of the trial, its possible benefits, and its potential risks. All recruited patients signed an informed consent form on the trial.

Random Assignment

The patients were randomly subdivided into two different groups. Those in one group were subjected to low-level

Reprint requests: Domenico Cuda, MD, Unità Operativa di Otorinolaringoiatria, Ospedale “G. da Saliceto,” Via Cantone del Cristo 40, I-29100 Italy. Phone: +39(0)523.303262; Fax: +39(0)523.303273; E-mail: d.cuda@ausl.pc.it

laser stimulation (LLS+, or the experimental group); the others, the control group, were designated as LLS-. All patients of both groups were treated with the same combined counseling protocol. Thus, the experimental group (LLS+) received combined counseling and low-level laser stimulation, and those in the control group received only the counseling combined with the faked stimulation device, which appeared identical to the active one but had no laser emission (placebo). Random assignment to treatment was carried out by one of the authors, but the actual type of stimulation applied was not revealed to the second author until assessment of the entire population was completed.

Low-Level Laser Stimulation

Patients in the experimental group received a device emitting laser cold light (TinniTool EarLaser, DisMark GmbH, Maur, Switzerland). The emission power was 5 mW, and the wavelength was 650 nm. The system was composed of an emitting body equipped with a probe to be placed at the entrance of the external auditory canal from where the laser ray was directed toward the eardrum. For more comfort during therapy, the laser was coupled to a wearable ear hook. Patients were trained to use the device for 20 minutes per day, each day for 3 months.

The placebo group of patients received a device identical to the active one in terms of appearance and weight; because the laser irradiation does not cause any sensation, it was impossible for any patient to detect the real nature of the stimulation received. The directions for use were the same as those given to patients in the LLS+ group.

Combined Counseling

Each patient was subjected to the same standardized protocol of combined counseling. This constituted 10 sessions of 40 minutes each regularly distributed during the 3-month treatment period. Combined counseling consisted of the combination of two different approaches: a cognitive and a psychosomatic approach. Cognitive counseling was based on tinnitus retraining therapy principles [2,3]. Our objective was to promote habituation and thus eliminate the problem by removing any negative association to tinnitus. It consisted of exhaustive discussions about the causes and the meaning of tinnitus and about the anatomy and physiology of ears and auditory pathways so as to promote understanding of the symptom and to demystify it.

The second component of combined counseling (i.e., the psychosomatic approach) focused on the particular emotional state of the patient and comes from the combination of hypnotic techniques with relaxation techniques based on respiration, proprioception, and insight

[4]. Stress-causing factors and the reactive reflexes associated with them are identified. The objective is to rehabilitate the cerebral center responsible for the perception of the problem by favoring filtering and blocking of the signal that causes the tinnitus. The hypnotic techniques used are those described by Erickson [5], aimed at developing a higher ability to handle the symptom by increasing the patient's reactive potential and by causing a "change" in the response to the symptom. The objective of hypnosis is to change the patient's behavior, sensory responses, and state of consciousness by providing new ways of thinking, feeling, and acting about the symptom. To meet these objectives, different resources taken from Erickson, such as metaphors and direct hypnosis, were used. In addition, we used relaxation techniques described by Jakobson [6]. This method consists of letting the patient contract muscle segments or groups and then letting those segments or groups progressively relax over a variable period of time. These exercises are effective in patients who are scarcely aware of their body and their tonic response.

Outcome Indicators

Patients were subjected to a general otological evaluation consisting of medical history, otomicroscopy, audiometry, and impedance audiometry. If necessary for diagnostic purposes, we carried out auditory brainstem response, electronystagmography, magnetic resonance imaging, and otoacoustic emission tests. Moreover, for descriptive purposes, we performed tinnitus tests (loudness and pitch match, minimum masking levels). The Tinnitus Handicap Inventory (THI), developed by Newman et al. [7], was given to patients at the beginning and at the end of the treatment. The THI scores were considered as rough scores (from 0 to 100) to classify severity. Classes of severity were codified as follows [8]: slight tinnitus (THI score, 0–25), medium (score, 26–50), severe (score, 51–75), and catastrophic (76–100).

Data Analysis

We drew up descriptive statistics for all variables. As to the differences between the groups, we performed the analysis of variance (ANOVA) for continuous variables, whereas we performed a chi-square analysis for single variables. We also conducted analysis through a statistics program (SPSS14).

RESULTS

Description of the Sample

Tinnitus was localized in the right ear in 7 patients (15.2%), in the left ear in 10 (21.8%), and bilaterally in

29 (63%). The symptom had been present for between 3 months and 45 years (mean, 6.4; SD, 8.8).

From an audiometric point of view, 7 patients had normal hearing (15.2%) and 21 (45.7%) had a slight sensorineural hearing loss with pure-tone threshold average (PTA) at 0.5–4 kHz <30 dB). Therefore, 60.9% of patients had no clinically significant hearing impairment, whereas the other cases were defined as follows: slight to moderate hearing loss (PTA, 31–40 dB) in 6 patients (13%); moderate hearing loss (PTA, 41–60 dB) in 8 (17.4%); moderate to severe hearing loss (PTA, 61–80 dB) in 1 patient (2.2%); and severe hearing loss (PTA, >81 dB) in 3 patients (6.5%). No patient had conductive or mixed loss. All patients affected by significant hearing loss regularly wore air-conduction hearing aids.

The mean loudness was 6.1 dB sound level (SL) (SD, 4.9). The mean pitch estimation was 4,700 Hz (range, 1,000–12,000; SD, 2,700). The minimum masking level was 12.8 dB (SD, 8.9). The pretreatment THI score was 49.1 (range, 8–94; SD, 22.6). The disorder classification was as follows: slight tinnitus in 9 (19.6%), medium in 16 (34.8%), serious in 12 (26.1%), and catastrophic in 9 (19.6%). Twenty patients were assigned to the LLS– group and 26 to the LLS+ group. All patients completed the treatment protocol.

Differences Between Groups

Entire Sample

No patient presented with deterioration or other significant changes in the audiometric threshold at the end of the trial. Moreover, we observed no otomicroscopic lesion of the auditory canals or eardrums. The audiometric characteristics of the tinnitus were unchanged after treatment: loudness match, 5.3 dB (SD, 5.2; not significant [NS]); pitch match, 4,200 Hz (SD, 3,200; NS); and minimum masking level, 10.8 dB (SD, 10.1; NS).

At the end of the treatment period, the average THI score was 36.2 (range, 8–84; SD, 19.9). Tinnitus was graded as slight in 14 patients (30.4%), medium in 21 (45.7%), severe in 9 (19.6%), and catastrophic in 2 patients (4.3%). The difference between pre- and post-treatment THI scores was statistically significant ($t = 2.882; p = .005$). In terms of THI grading, the pre- and posttreatment differences were also statistically significant (chi-squared test, $p < .01$).

LLS– Versus LLS+ Groups

A synthesis of the statistical analysis for continuous variables is shown in Table 1. Patient age was different in the two subgroups in a statistically significant way ($p < .000$): Those in the experimental group (LLS+) were younger than those in the LLS– group (50.3 vs. 64.4 years). The duration of tinnitus and the pre- and

Table 1. Analysis of Variance Relative to Continuous Variables in a Group of Patients with Disturbing Tinnitus Undergoing Treatment with Counseling and Low-Level Laser (LLS+ [$n = 26$]) or Counseling Only (LLS– [$n = 20$])

Parameter	Mean	SD	Min-imum	Max-imum	F	Signif-icance
Age (years)						
LLS–	64.4	14.1	28	83	15.9	$p < .01$
LLS+	50.3	9.8	31	76		
Total	56.4	13.6	28	83		
Duration						
LLS–	8.4	10.6	0.3	45	1.9	NS
LLS+	4.8	6.8	0.3	26		
Total	6.4	8.8	0.3	45		
THI pretreatment						
LLS–	43.1	22.1	8	86	2.5	NS
LLS+	53.6	22.3	14	94		
Total	49.1	22.6	8	94		
THI posttreatment						
LLS–	35.8	18.9	8	74	0.02	NS
LLS+	36.6	21.1	10	84		
Total	36.2	19.9	8	84		
Delta THI						
LLS–	7.3	15.4	–20	42	4.1	$p < .05$
LLS+	17.1	16.7	–18	48		
Total	12.8	16.7	–20	48		

NS = not significant.

posttreatment THI scores did not significantly differ between the two subgroups. On the contrary, the delta THI (defined for each patient as the difference between pre- and post-treatment THI score) was statistically greater in the LLS+ (experimental) than in the LLS– group (17.1 vs. 7.3; $p < .05$).

Intergroup differences (LLS– and LLS+) between nominal variables were analyzed with the chi-squared test. No statistically significant difference for tinnitus side, auditory threshold class, or tinnitus classification were found.

In Figure 1, pre- and posttreatment differences in tinnitus classification are shown. Taking into consideration the total population, the tinnitus grading remained unchanged in 18 patients (39.2%), whereas it improved in 23 patients (50%), improving by one grade in 19 patients (41.3%) and by two grades in 4 patients (8.7%). In only 5 patients (10.87%) was there a one-grade worsening. In the placebo group (LLS–), the grading remained unchanged in 9 patients (45%), whereas it improved in 7 (35%)—a one-grade improvement occurred in 6 patients (30%) and a two-grade improvement in 1 (5%)—and worsened in 4 patients (20%). In the experimental group (LLS+), there was an overall improvement in 16 patients (61.6%), by one grade in 13 patients (50%) and by

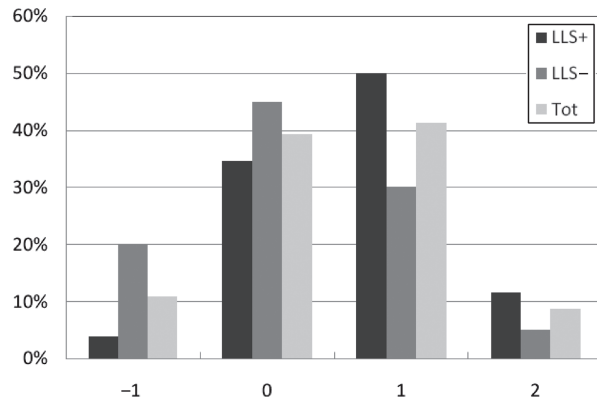


Figure 1. Differences in pre- and posttreatment tinnitus severity grades. Minus 1 (–1) indicates grade worsening; 0 indicates that the grade is unchanged; and 1 and 2 indicate an improvement by one or two grades, respectively. (LLS+ = patients treated with active laser; LLS– = placebo group; Tot = entire group.)

two grades in 3 patients (11.6%). Also in this group, the grade worsened in 1 patient (3.8%) and remained unchanged in the other 9 (34.6%).

DISCUSSION

In the present study, a nonselected group of patients affected by chronic disturbing tinnitus was treated with a combined counseling method integrating hypnotherapeutic and muscle relaxation techniques. The THI score, the main tinnitus severity index considered here, was significantly reduced after treatment, whereas audiometric characteristics of tinnitus were unchanged. The effectiveness of counseling on the treatment of tinnitus is already known [2,3]. The effect of the various relaxation techniques in patients suffering from chronic tinnitus has been assessed in a number of controlled trials [9–13]; although no final proof exists of the effectiveness of these techniques on the perception of tinnitus, a reduction in the symptoms associated with stress and anxiety—and thus an improvement in the acceptance of the symptoms—was observed. The effect of hypnosis has been documented in different studies [14–18], sometimes with conflicting results but with a general trend toward higher tolerance to symptoms by those involved in the research.

In our study, counseling and hypnotherapy had a generally good effect on the entire observed group. Relaxation techniques were used also at home, in difficult moments and to aid the subject in getting to sleep, which is a critical moment for patients affected by tinnitus because the perception of sounds in the ear is facilitated by silence. Elderly patients showed diligence to and understanding of the therapeutic program. They enjoyed increasing their care for their body and finding new strat-

egies to reduce concomitant physical troubles (dyspnea, muscle-tension pain due to arthritis). Having more spare time, these patients could exercise at home more regularly than younger people. Regular exercise became an important part of their daily life and led to positive thinking. The chance to talk was perceived by these patients as a sign of care, which balanced the frequent absence of affection for the elderly. The opportunity to practice a therapeutic technique that could help the patients to relax and observe the single elements that compose their pathological “syndrome” acted as a tranquilizer: as a matter of fact, the fragmentation of symptoms reduced their impact.

Our study also confirmed a significant difference in the benefit of treatment between the LLS+ and LLS– groups. The random anomalous distribution of age that resulted in the group subject to laser stimulation being younger than the placebo group must be considered (as the sampling procedure did not take into account each patient’s age); this result must be traced back to the different stimulation applied. No other difference was revealed between subgroups LLS+ and LLS– as regards the characteristics of the population, such as the duration of symptoms or the distribution according to hearing loss levels, tinnitus side, or perceived pretreatment seriousness. Therefore, 61.6% of the patients treated with laser improved by at least one class as compared to 35% of the placebo group (see Fig. 1). The average improvement in terms of THI score was 17.1 vs 7.3, respectively.

The results of low-level laser stimulation in the literature are somewhat contradictory. For example, Partheniadis-Stumpf et al. [19] reported an improvement in 3 patients, whereas 5 were uncertain about the results of their treatment and, in 20 patients, tinnitus remained unchanged. In their trial, however, the administration of a drug (Tebonin) was combined with a stimulation protocol that involved 12 laser applications, each of a 10-minute duration, to the top of the mastoid bone. The trial lasted 3 weeks, and the success criterion was based solely on patients’ judgment [19]. Therefore, the protocol cannot be compared to that of our current study.

Shiomi et al. [20] used transmeatal stimulation that was more powerful than that used in the present trial (40 mW, with a wavelength of 830 nm). The protocol used by Shiomi’s group involved irradiation for 9 minutes per time for 10 or more weeks. The 28 patients recruited for the trial had to give a score to their symptoms on a 5-point scale before and after treatment had concluded. Because an improvement in loudness and annoyance level was reported in 55% and 58%, respectively, the authors concluded that laser therapy deserves a trial in patients affected by untreatable tinnitus.

Interestingly, a clinical trial by Mirz et al. [21] led to opposite conclusions. This controlled trial involved

50-mW laser stimulation (wavelength 830 nm) and a placebo group. The protocol called for transmeatal irradiation for 10 minutes per session. Among the 49 patients recruited, no statistically significant difference was revealed between the placebo and the active groups for a series of indicators, including visual analog scales for loudness, annoyance, and attention, as well as THI score [21].

Similar results were described by Nakashima et al. [22]. The irradiation was transmeatal in this case also, and the power used was 60 mW supplied for 6 minutes once weekly for 4 weeks. The result indicators considered were based on a questionnaire submitted to 45 recruited patients. Between the active and the placebo group, no differences were reported in terms of loudness, duration, quality, and annoyance of tinnitus. Moreover, a patient receiving irradiation presented with acute hearing deterioration after the third irradiation session. Unlike the results of Nakashima et al. [22], we recorded no cases of deterioration of the auditory threshold in our sample. It must be emphasized that our protocol was different, using lower power for a longer period (5 mW for 20 minutes) than that employed by Nakashima's team.

The importance of technical aspects was emphasized by Tauber et al. [23], who were able to verify positive effects in a sample of 38 patients affected by chronic tinnitus through an appropriate control of dosimetric variables. In Tauber's trial, power emissions were lower than those used in the trials mentioned previously (7.8 and 20 mW).

Gungor et al. [24] carried out a controlled trial with an application protocol similar to that of our trial. The laser power was 5 mW and the wavelength 650 nm. Treatment application was transmeatal for 15 minutes daily for a week. The 45 recruited patients responded to a questionnaire in which the symptoms were classified according to a 5-point scale before and after treatment. Tinnitus loudness, duration, and annoyance level improved in 48.8%, 57.7%, and 55.5% of the patients, respectively, with active laser, whereas in the placebo group no significant change was reported. Indirect support for the conclusions of that trial comes from a recent study carried out by Siedentopf et al. [25] who documented, using functional magnetic resonance imaging, the activation of different cerebral areas (left superior frontal gyrus, right middle frontal gyrus, and right superior parietal lobe) through low-level transmeatal laser stimulation. The placebo application, randomly alternated to laser stimulation and indistinguishable by the patient, did not determine any neurological activation. Surprisingly, the activated cerebral areas correspond to those affected in tinnitus patients, as shown by positron emission tomography surveys [26,27].

The low-level laser action mechanism is biophysiological rather than thermal [28]. The primary site of neu-

ronal absorption is represented by mitochondria, with consequent release from cytoplasm of H⁺ protons. The cellular membrane permeability for Na and K is reduced, with consequent reduction in action potential [29]. The effect of inhibiting the action potential was shown through a trial after laser stimulation of the cochlea through the round window [20]. Another postulated mechanism is the increase of blood flow [30] attributable to sympathetic neural inhibition. However, alternative mechanisms, such as an increase in cell proliferation [31], adenosine triphosphate synthesis [32], and collagen [33] are also possibilities.

The limited sample studied (in any case limited to tens of patients) and the differences in application protocols do not allow a careful comparison of our work with other studies. The results of our trial should therefore be confirmed through a larger, multicentric controlled clinical trial with an accurate definition of the indicators. Nonetheless, preliminary data suggest a favorable effect of low-level laser stimulation in the otologist's therapeutic equipment.

REFERENCES

1. Jastreboff PJ. Phantom auditory perception (tinnitus): Mechanisms of generation and perception. *Neurosci Res* 8(4):221–254, 1990.
2. Jastreboff PJ, Gray WC, Gold SL. Neurophysiological approach to tinnitus patients. *Am J Otol* 17(2):236–240, 1996.
3. Hazell JW. Tinnitus: Psychosomatic Aspects of Complex Chronic Tinnitus (Occurrence, Effects, Diagnosis and Treatment). In Goebel G (ed), *Tinnitus—Psychosomatic Aspects of Complex Chronic Tinnitus. Occurrence, Effects, Diagnosis and Treatment*. London: Quintessence, 1998.
4. Colombo C, De Caria A. Considerazioni e innovazioni nel trattamento degli acufeni con tecniche di rilassamento profondo e “sound generators.” *Riv Med Ital Psicoterap Ipnosi* 15(1):105–128, 2003.
5. Erickson MH. *Creative Choice in Hypnosis: The Seminars, Workshops and Lectures of Milton H. Erickson*. New York: Irvington, 1992.
6. Jacobson E. Neuromuscular controls in man: Methods of self direction in health and in disease. *Am J Psychol* 68(4): 549–561, 1955.
7. Newman CW, Jacobson GP, Spitzer JB. Development of the Tinnitus Handicap Inventory. *Arch Otolaryngol Head Neck Surg* 122:143–148, 1996.
8. Cuda D. *Acufeni: Diagnosi e terapia. Quaderni Monografici di Aggiornamento*. Roma: Edizioni A.O.O.I., 2004. Retrieved from <http://www.aooi.it/acufe.pdf>.
9. Kirsch CA, Blanchard EB, Parnes SM. A multiple-baseline evaluation of the treatment of subjective tinnitus with relaxation training and biofeedback. *Biofeedback Self Regul* 12(4):295–312, 1987.

10. Davies S, McKenna L, Hallam R. Relaxation and cognitive therapy: A controlled trial in chronic tinnitus. *Psychol Health* 10:129–143, 1995.
11. Kröner-Herwig B, Hebing G, van Rijn-Kalkmann U, et al. The management of chronic tinnitus—comparison of a cognitive-behavioural group training with yoga. *J Psychosom Res* 39(2):153–165, 1995.
12. Winter B, Nieschalk M, Stoll W. Effects of relaxation therapy as group and individual treatment of chronic tinnitus. *Psychother Psychosom Med Psychol* 46(3–4):147–152, 1996.
13. Dineen R, Doyle J, Bench J. Managing tinnitus: A comparison of different approaches to tinnitus management training. *Br J Audiol* 31(5):331–344, 1997.
14. Marks NJ, Karl H, Onisiphorou C. A controlled trial of hypnotherapy in tinnitus. *Clin Otolaryngol Allied Sci* 10(1):43–46, 1985.
15. Attias J, Shemesh Z, Sohmer H, et al. Comparison between self-hypnosis, masking and attentiveness for alleviation of chronic tinnitus. *Audiology* 32(3):205–212, 1993.
16. Mason JD, Rogerson DR, Butler JD. Client centered hypnotherapy in the management of tinnitus: Is it better than counseling? *J Laryngol Otol* 110(2):117–120, 1996.
17. Kaye JM, Marlowe FI, Ramchandani D, et al. Hypnosis as an aid for tinnitus patients. *Ear Nose Throat J* 73(5):309–312, 315, 1994.
18. Ross UH, Lange O, Unterrainer J, Laszig R. Ericksonian hypnosis in tinnitus therapy: Effects of a 28-day inpatient multimodal treatment concept measured by Tinnitus-Questionnaire and Health Survey SF-36. *Eur Arch Otorhinolaryngol* 264(5):483–488, 2007.
19. Partheniadis-Stumpf M, Maurer J, Mann W. Soft laser therapy in combination with Tebonin IV in tinnitus. *Laryngorhinootologie* 72(1):28–31, 1993.
20. Shiomi Y, Takahashi H, Honjo I, et al. Efficacy of transmeatal low power laser irradiation on tinnitus: A preliminary report. *Auris Nasus Larynx* 24(1):39–42, 1997.
21. Mirz F, Pedersen B, Ishizu K, et al. Positron emission tomography of cortical centers of tinnitus. *Hear Res* 134(1–2):133–144, 1999.
22. Nakashima T, Ueda H, Misawa H, et al. Transmeatal low-power laser irradiation for tinnitus. *Otol Neurotol* 23(3):296–300, 2002.
23. Tauber S, Schorn K, Beyer W, Baumgartner R. Transmeatal cochlear laser (TCL) treatment of cochlear dysfunction: A feasibility study for chronic tinnitus. *Lasers Med Sci* 18(3):154–161, 2003.
24. Gungor A, Dogru S, Cincik H, et al. Effectiveness of transmeatal low power laser irradiation for chronic tinnitus. *J Laryngol Otol* 12:1–5, 2007.
25. Siedentopf CM, Ischebeck A, Haala IA, et al. Neural correlates of transmeatal cochlear laser (TCL) stimulation in healthy human subjects. *Neurosci Lett* 16(411):189–193, 2007.
26. Lockwood AH, Salvi RJ, Coad ML, et al. The functional neuroanatomy of tinnitus: Evidence for limbic system links and neural plasticity. *Neurology* 51(2):647–648, 1998.
27. Mirz F, Zachariae R, Andersen SE, et al. The low-power laser in the treatment of tinnitus. *Clin Otolaryngol Allied Sci* 24(4):346–354, 1999.
28. Rochkind S, Nissan M, Lubart R, et al. The in-vivo-nerve response to direct low-energy-laser irradiation. *Acta Neurochir (Wien)* 94:74–77, 1988.
29. Karu T. Molecular mechanism of the therapeutic effect of low-intensity laser irradiation. *Lasers Life Sci* 2:53–74, 1988.
30. Schaffer M, Bonel H, Sroka R, et al. Effects of 780 nm diode laser irradiation on blood microcirculation: Preliminary findings on time-dependent T₁-weighted contrast-enhanced magnetic resonance imaging (MRI). *J Photochem Photobiol B* 54:55–60, 2000.
31. Hans HFI, Breugel V, Bar D. Power density and exposure time of He–Ne laser irradiation are more important than total energy dose in photobiomodulation of human fibroblasts in vitro. *Lasers Surg Med* 12:528–537, 1992.
32. Passarella S, Casamassima E, Molinari S, et al. Increase of proton electrochemical potential and ATP synthesis in rat liver mitochondria irradiated in vitro by helium-neon laser. *FEBS Lett* 175:95–99, 1984.
33. Reddy GK, Stehno-Bittel L, Enwemeka CS. Laser photostimulation of collagen production in healing rabbit Achilles tendons. *Lasers Surg Med* 281–287, 1998.