

Low-level laser therapy for tinnitus (Protocol)

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
BACKGROUND	2
OBJECTIVES	4
METHODS	4
ACKNOWLEDGEMENTS	6
REFERENCES	7
ADDITIONAL TABLES	11
APPENDICES	12
HISTORY	12
CONTRIBUTIONS OF AUTHORS	12
DECLARATIONS OF INTEREST	13
SOURCES OF SUPPORT	13

[Intervention Protocol]

Low-level laser therapy for tinnitus

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effectiveness of low-level laser therapy for the treatment of subjective idiopathic tinnitus.

BACKGROUND

This is one of a number of tinnitus reviews produced by the Cochrane Ear, Nose & Throat Disorders Group, which use a standard Background. The following paragraphs ('Description of the condition') are based on earlier work in the following reviews and reproduced with permission: [Baldo 2006](#); [Bennett 2007](#); [Hilton 2004](#); [Hobson 2010](#); [Phillips 2010](#).

Description of the condition

Tinnitus can be described as the perception of sound in the absence of external acoustic stimulation. For the patient it may be trivial or it may be a debilitating condition ([Luxon 1993](#)). The quality of the perceived sound can vary enormously from simple sounds such as whistling or humming to complex sounds such as music. The patient may hear a single sound or multiple sounds. Tinnitus may be perceived in one or both ears, within the head or outside the body. The symptom may be continuous or intermittent. Tinnitus is described in most cases as subjective - meaning that it cannot be heard by anyone other than the patient. While, for the patient, this perception of noise is very real, because there is no corresponding external sound it can be considered a phantom, or false, perception. Objective tinnitus is a form of tinnitus which can be detected by an examiner, either unaided or using a listening aid such as a stethoscope or microphone in the ear canal. This is much less common and usually has a definable cause such as sound generated by blood flow in or around the ear or unusual activity of the tiny muscles within the middle ear. Tinnitus may be associated with normal hearing or any degree of hearing loss and can occur at any age.

It is important to distinguish between clinically significant and non-significant tinnitus ([Davis 2000](#)) and several different classifications have been proposed ([Dauman 1992](#); [McCombe 2001](#); [Stephens 1991](#)). Dauman, for example, makes a distinction between 'normal' (lasting less than five minutes, occurring less than once a week and experienced by most people) and 'pathological' tinnitus (lasting more than five minutes, occurring more than once a week and usually experienced by people with hearing loss).

Aetiology

Almost any form of disorder involving the outer, middle or inner ear or the auditory nerve may be associated with tinnitus ([Brummett 1980](#); [Shea 1981](#)). However, it is possible to have severe tinnitus with no evidence of any aural pathology. Conversely, tinnitus can even exist without a peripheral auditory system: unilateral tinnitus is a common presenting symptom of vestibular schwannomas (acoustic neuromas), which are rare benign tumours of the vestibulo-cochlear nerve. When these neuromas are removed by a translabyrinthine route, the cochlear nerve can be severed. Despite the effective removal of their peripheral auditory mechanisms, 60% of these patients retain their tinnitus postoperatively

([Baguley 1992](#)). This suggests the fundamental importance of the central auditory pathways in the maintenance of the symptom, irrespective of trigger.

Many environmental factors can also cause tinnitus. The most relevant and frequently reported are:

- acute acoustic trauma (AAT) (for example, explosions or gunfire) ([Christiansson 1993](#); [Chung 1980](#); [Melinek 1976](#); [Mrena 2002](#); [Tommel 1999](#));
- airbag inflation ([Saunders 1998](#)); toy-pistols ([Fleischer 1999](#));
- exposure to occupational noise; 'urban noise pollution' ([Alberti 1987](#); [Axelsson 1985](#); [Chouard 2001](#); [Daniell 1998](#); [Griest 1998](#); [Kowalska 2001](#); [McShane 1988](#); [Neuberger 1992](#); [Phoon 1993](#)); and
- exposure to recreational and amplified music ([Becher 1996](#); [Chouard 2001](#); [Lee 1999](#); [Metternich 1999](#))

Pathophysiology

Over 50 years ago, Heller and Bergman demonstrated that if 'normal' people (with no known cochlear disease) were placed in a quiet enough environment, the vast majority of them would experience sounds inside their head. They concluded that tinnitus-like activity is a natural phenomenon perceived by many in a quiet enough environment ([Heller 1953](#)).

Mazurek has shown that pathologic changes in the cochlear neuro-transmission, e.g. as a result of intensive noise exposure or ototoxic drugs, can be a factor in the development of tinnitus ([Mazurek 2007](#)).

In the 'neurophysiological model' of tinnitus ([Jastreboff 1990](#); [Jastreboff 2004](#)) it is proposed that tinnitus results from the abnormal processing of a signal generated in the auditory system. This abnormal processing occurs before the signal is perceived centrally. This may result in 'feedback', whereby the annoyance created by the tinnitus causes the individual to focus increasingly on the noise, which in turn exacerbates the annoyance and so a 'vicious cycle' develops. In this model tinnitus could therefore result from continuous firing of cochlear fibres to the brain, from hyperactivity of cochlear hair cells or from permanent damage to these cells being translated neuronally into a 'phantom' sound-like signal that the brain 'believes' it is hearing. For this reason tinnitus may be compared to chronic pain of central origin - a sort of 'auditory pain' ([Briner 1995](#); [Sullivan 1994](#)).

The relationship between the symptom of tinnitus and the activity of the prefrontal cortex and limbic system has been emphasised. The limbic system mediates emotions. It can be of great importance in understanding why the sensation of tinnitus is in many cases so distressing for the patient. It also suggests why, when symptoms are severe, tinnitus can be associated with major depression, anxiety and other psychosomatic and/or psychological disturbances, leading to a progressive deterioration of quality of life ([Lockwood 1999](#); [Sullivan 1989](#); [Sullivan 1992](#); [Sullivan 1993](#)).

Prevalence

Epidemiological data reports are few. The largest single study was undertaken in the UK by the Medical Research Council Institute of Hearing Research and was published in 2000 (Davis 2000). This longitudinal study of hearing questioned 48,313 people; 10.1% described tinnitus arising spontaneously and lasting for five or more minutes at a time and 5% described it as moderately or severely annoying. However, only 0.5% reported tinnitus having a severe effect on their life. This is another of the paradoxes of tinnitus: the symptom is very common but the majority of people who experience it are not particularly concerned by it. These figures from the UK are broadly consistent with data collected by the American Tinnitus Association (ATA) which suggests that tinnitus may be experienced by around 50 million Americans, or 17% of the US population (ATA 2004). Data also exist for Japan, Europe and Australia (Sindhusake 2003), and estimates suggest that tinnitus affects a similar percentage of these populations, with 1% to 2% experiencing debilitating tinnitus (Seidman 1998). The Oregon Tinnitus Data Archive (Oregon 1995) contains data on the characteristics of tinnitus drawn from a sample of 1630 tinnitus patients. The age groups with the greater prevalence are those between 40 and 49 years (23.9%) and between 50 and 59 years (25.6%).

Olszewski showed in his study that the risk of tinnitus increases in patients over 55 years old who suffer from metabolic conditions and cervical spondylosis (Olszewski 2008).

Diagnosis

Firstly a patient with tinnitus may undergo a basic clinical assessment. This will include the relevant otological, general and family history, and an examination focusing on the ears, teeth and neck and scalp musculature. Referral to a specialist is likely to involve a variety of other investigations including audiological tests and radiology. Persistent, unilateral tinnitus may be due to a specific disorder of the auditory pathway and imaging of the cerebello-pontine angle is important to exclude, for example, a vestibular schwannoma (acoustic neuroma) - a rare benign tumour of the cochleo-vestibular nerve. Other lesions, such as glomus tumours, meningiomas, adenomas, vascular lesions or neuro-vascular conflicts may also be detected by imaging (Marx 1999; Weissman 2000).

Treatment

At present no specific therapy for tinnitus is acknowledged to be satisfactory in all patients. Many patients who complain of tinnitus, and also have a significant hearing impairment, will benefit from a hearing aid. Not only will this help their hearing disability but the severity of their tinnitus may be reduced.

A wide range of therapies have been proposed for the treatment of tinnitus symptoms. Pharmacological interventions used include cortisone (Koester 2004), vasodilators, benzodiazepines, lidocaine

and spasmolytic drugs. The use of anticonvulsants in treating tinnitus is the subject of a Cochrane review (Hoekstra 2011). Antidepressants are commonly prescribed for tinnitus. However, two reviews (Baldo 2006; Robinson 2007) showed that there is no indication that tricyclic antidepressants have a beneficial effect.

Although a number of studies have suggested that Ginkgo biloba may be of benefit in the treatment of tinnitus (Ernst 1999; Holger 1994; Rejali 2004), a Cochrane review showed that there was no evidence that it is effective where tinnitus was the primary complaint (Hilton 2004).

Hyperbaric oxygen therapy (HBOT) can improve oxygen supply to the inner ear which it is suggested may result in an improvement in tinnitus, however a Cochrane review found insufficient evidence to support this (Bennett 2007).

Studies have been carried out into the effect of cognitive behavioural therapy (CBT) on tinnitus (Andersson 1999). Another Cochrane review has shown that CBT can have an effect on the qualitative aspects of tinnitus and can improve patients' ability to manage the condition (Martinez-Devesa 2010).

Other options for the management of patients with tinnitus include transcranial magnetic stimulation (Meng 2011), tinnitus masking (use of 'white noise' generators) (Hobson 2010), music therapy (Argstatter 2008), reflexology, hypnotherapy and traditional Chinese medicine (TCM), including acupuncture (Li 2009).

Description of the intervention

Laser was discovered in the 1960s. Laser is light that is generated by high-intensity electrical stimulation of a medium, which can be a gas, liquid, crystal, dye or semiconductor (Tunér 1999). The light produced consists of coherent beams of single wavelengths in the visible to infrared spectrum, which can be emitted in a continuous wave or pulsed mode (Bjordan 2007; Bjordan 2008). Mester first reported the earliest clinical application of the low-level laser in 1972 (Mester 1972). Since then, low-level laser therapy (LLLT) has come to the forefront of clinical research. Hundreds of randomised, double-blind, placebo-controlled phase III clinical trials have been published from over a dozen countries (Kaviani 2011; Saayman 2011; Silva 2011).

Low-level laser therapy (LLLT) uses low-powered laser light in the range of 1 to 1000 mW, at wavelengths from 632 to 1064 nm, to stimulate a biological response. LLLT uses laser to aid tissue repair (Woodruff 2004), relieve pain (Enwemeka 2004) and stimulate acupuncture points (Siendentopf 2002). Surgical applications of laser ablate tissue by intense heat and are different from LLLT, which uses light energy to modulate cell and tissue physiology to achieve therapeutic benefit without a macroscopic thermal effect (sometimes termed cold laser). LLLT is non-invasive, painless and can be easily administered in primary care settings.

LLLT acts by inducing a photochemical reaction in the cell, a process referred to as biostimulation or photobiomodulation (Hashmi

2010). It is an irradiation technique that has the ability to induce biological processes using photon energy. There are studies showing proliferation and angiogenesis after irradiation in skeletal muscle tissue cells post-myocardial infarction. Most evidence of efficacy is based on the increase in energy state and the activation of mitochondrial pathways. It has been reasonably well established that mitochondria are a principal intracellular target of red and near infrared light (Karu 1989). Cytochrome C oxidase (unit IV of the mitochondrial respiratory chain) is a chromophore that absorbs light as far into the infrared as 1000 nm (Szundi 2001). In recent years, LLLT has been widely used in the treatment of tinnitus. The laser emits dual wavelength beams which are red and near infrared. These laser beams are cool to the touch and do not cause discomfort. They are aimed into the auditory canal and through the mastoid bone behind the ear. The patients are awake during the period of therapy. The wavelength nature of these lasers allows them to penetrate tissue. Although the laser beams lose intensity rapidly, they can have an effect on tissues 2 to 5 cm inside the body. The mechanism of action of low-level laser on the inner ear and on tinnitus is not well understood. Previous studies evaluating low-level laser for the treatment of tinnitus have been equivocal, with both positive (Hahn 2001; Plath 1995; Shiomi 1997; Wilden 1996) and negative effects (Mirz 1999; Nakashima 2002; Tauber 2003; Teggi 2009) reported. The incidence of adverse effects of LLLT is low and similar to that of placebo, with no reports of serious events (Nakashima 2002).

How the intervention might work

Several hypotheses have been proposed for the mechanism of action of LLLT. The prevailing opinion is that the respiratory chain plays a central role in the effect induced by laser therapy (Rhee 2011). Laser energy in the red and near infrared light spectrum is capable of penetrating tissue. It stimulates mitochondria in the cells to produce energy through the production of adenosine triphosphate (ATP) (Karu 1995). Mitochondria are the power supplies of all cells; they metabolise fuel and produce energy for the cell in the form of ATP. It has been reported that LLLT irradiation increases the production of ATP (Oron 2007). Increased ATP production may lead to enhanced cell metabolism, promoting the damage recovery process, returning cells to a healthy state and reversing many degenerative conditions. For ear disorders, low-level laser has been reported to alter the collagen organisation within the cochlea, especially within the basilar membrane. This should increase the stiffness of the basilar membrane (Wenzel 2004; Wenzel 2007). Also, LLLT has a beneficial effect on the recovery of cochlear hair cells after acute hair cell loss (Rhee 2011), increases cell proliferation (van Breugel 1992), synthesis of ATP (Passarella 1984) and collagen (Reddy 1998), release of growth factors (including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF) and ciliary neurotrophic factor (CNTF))

(Kipshidze 2001; Yu 1994; Yazdani 2012), promotes local blood flow in the inner ear associated with suppression of the sympathetic nerve action potential, and activates repair mechanisms in the inner ear through photochemical and photophysical stimulation of the hair cell mitochondria (Karu 1986).

Additionally, studies have shown that laser leads to activation of related cortical areas in healthy subjects. The mechanism leading to the observed activated neuronal network by means of transmeatal cochlear laser (TCL) is vague (Siedentopf 2007). It cannot be explained by a supra-sensory stimulation of the tympanic membrane, since subjects are not able to differentiate between real and placebo stimulation.

Different low-level laser therapy studies have focused on the determination and the modulation of irradiation parameters that seem to play a pivotal role in its effectiveness (Amaral 2001; Basford 1995; Belkin 1994; Gungor 2008; Rochkind 1987; Rochkind 1992; Tauber 2003). The biological effects of low-level laser therapy are supposed to depend largely on well-controlled parameters, e.g. wavelength, waveform, power, dosage per site, duration of irradiation, type of irradiated cell and time interval between injury and irradiation.

Why it is important to do this review

The effects of low-level laser directed at the auditory canal or the mastoid bone behind the ear are not known (Hahn 2001; Mirz 1999; Nakashima 2002; Plath 1995; Shiomi 1997; Tauber 2003; Teggi 2009; Wilden 1996). Therefore this Cochrane review will provide an up-to-date, detailed analysis of the current evidence available.

OBJECTIVES

To assess the effectiveness of low-level laser therapy for the treatment of subjective idiopathic tinnitus.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials.

Types of participants

Adults in whom there is a complaint of persistent, distressing, subjective tinnitus of any aetiology.

Types of interventions

Studies where the patients received low-level laser therapy. Comparisons will include the following.

- Low-level laser therapy versus placebo
- Low-level laser therapy versus drug/other therapy

Types of outcome measures

Primary outcomes

- Improvement in tinnitus severity and disability, measured by a validated tinnitus-specific questionnaire. Commonly used tinnitus questionnaires are listed in [Table 1 \(Budd 1995; Erlandsson 1992\)](#).

Secondary outcomes

- Improvement of quality of life
- Change in socio-economic impact associated with work
- Change in anxiety and depression disorders
- Change in psychoacoustic parameters
- Change in tinnitus loudness
- Change in overall severity of tinnitus
- Change in thresholds on pure-tone audiometry
- Adverse effects of treatment

Search methods for identification of studies

We will conduct systematic searches for randomised controlled trials. There will be no language, publication year or publication status restrictions. We may contact original authors for clarification and further data if trial reports are unclear, and we will arrange translations of papers where necessary.

Electronic searches

We will identify published, unpublished and ongoing studies by searching the following databases from their inception: the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*); PubMed; EMBASE; CINAHL; LILACS; KoreaMed; IndMed; PakMediNet; CAB Abstracts; Web of Science; BIOSIS Previews; ISRCTN; ClinicalTrials.gov; ICTRP and Google.

We will model subject strategies for databases on the search strategy designed for CENTRAL (see [Appendix 1](#)). Where appropriate, we will combine subject strategies with adaptations of the highly sensitive search strategy designed by the Cochrane Collaboration for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0, Box 6.4.b. ([Handbook 2011](#))).

Searching other resources

We will scan the reference lists of identified publications for additional trials and contact trial authors if necessary. In addition, we will search PubMed, TRIPdatabase, *The Cochrane Library* and Google to retrieve existing systematic reviews relevant to this systematic review, so that we can scan their reference lists for additional trials. We will search for conference abstracts using the Cochrane Ear, Nose and Throat Disorders Group Trials Register.

Data collection and analysis

Selection of studies

Two authors (Zhe Peng, Xiu Qi Chen) will independently review the titles, abstracts and keywords of all records retrieved to identify studies which meet the inclusion criteria outlined above. We will resolve disagreements by consensus.

Data extraction and management

The same two review authors will carry out data extraction independently. Each review author will review approximately the same number of studies. We will use a standardised extraction form for data collection. Unresolved disagreement on inclusion, 'Risk of bias' assessment and data collection will be referred to the other two authors (Shusheng Gong, Chengfang Chen). Extracted data will include the following.

1. Study details: first author; year of publication; country of publication; publication type.
2. Study eligibility: type of study; participants; types of intervention; types of outcomes/measures.
3. Methods: study inclusion criteria; study exclusion criteria; detail of participants (age, sex, aetiology, hearing level, duration of tinnitus, severity of tinnitus); setting; study intervention (wave, session, frequency); study control; matching of interventions; compliance; similarity between groups; duration of follow-up.
4. Information on methods for 'Risk of bias' assessment.
5. Outcome: primary outcomes, secondary outcomes and other outcomes at the end of treatment and/or the end of follow-up. We will also extract the number and type of adverse events.
6. Conclusions.

We will contact authors for clarification and missing data information.

Assessment of risk of bias in included studies

Zhe Peng and Xiu Qi Chen will independently undertake assessment of the risk of bias of the included trials, with the following taken into consideration, as guided by the *Cochrane Handbook for Systematic Reviews of Interventions* ([Handbook 2011](#)):

- sequence generation;
- allocation concealment;
- blinding;
- incomplete outcome data;
- selective outcome reporting; and
- other sources of bias.

We will use the Cochrane ‘Risk of bias’ tool in Review Manager (RevMan) 5 (RevMan 2011), which involves describing each of these domains as reported in the trial and then assigning a judgement about the adequacy of each entry: ‘low’, ‘high’ or ‘unclear’ risk of bias.

Measures of treatment effect

We will analyse the data using Review Manager 5. We will assess the treatment effect for dichotomous data outcome measures using the risk ratio (RR) and for continuous data we will use the mean difference (MD), with 95% confidence intervals. We will combine data statistically if they are available and of sufficient quality and in the absence of significant heterogeneity.

Unit of analysis issues

To protect the accuracy of the results, we will only include randomised controlled trials. We will not include other non-standard designs such as cross-over trials and cluster-randomised trials.

Dealing with missing data

We will contact authors for missing data information. If the data are missing at random, analyses based on the available data will tend to be unbiased; if the data are said to be ‘not missing at random’, publication bias and selective reporting bias may exist. The principal options for dealing with missing data are based on the recommendations in the *Cochrane Handbook for Systematic Reviews of interventions*, Chapter 16 (Handbook 2011).

Assessment of heterogeneity

We will assess clinical heterogeneity by examining types of participants (e.g. cause of tinnitus), interventions and outcomes in each study. We will assess statistical heterogeneity among trials by inspecting the forest plots and using the Chi² test and the I² statistic. When interpreting the I² statistic, we will use the following thresholds:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

The importance of the observed value of the I² statistic depends on (i) the magnitude and direction of effects and (ii) the strength of evidence for heterogeneity (e.g. P value from the Chi² test or a confidence interval for I²) (Handbook 2011).

Assessment of reporting biases

We will test for potential publication bias using a funnel plot or other corrective analytical methods, depending on the number of clinical trials included in the systematic review. We will attempt to reduce any effects of reporting bias by obtaining and including missing trial data and data from unpublished trials where possible.

Data synthesis

A pooled statistical analysis of treatment effects will proceed only in the absence of significant clinical or statistical heterogeneity. Where it is appropriate to pool data and heterogeneity is detected, we will use the random-effects model. We will analyse the clinical heterogeneity of the included trials to determine whether it is appropriate to carry out the meta-analysis. If the trial data cannot be pooled, we will describe the outcomes in the text of the review.

Subgroup analysis and investigation of heterogeneity

No subgroup analyses are planned.

Sensitivity analysis

We will perform sensitivity analyses by repeating the analysis excluding internal reports and conference abstracts. We will use study quality in a sensitivity analysis.

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REFERENCES

Additional references

Alberti 1987

Alberti PW. Tinnitus in occupational hearing loss: nosological aspects. *Journal of Otolaryngology* 1987;**16**(1): 34–5.

Amaral 2001

Amaral AC, Parizotti NA, Salvini TF. Dose-dependency of low-energy HeNe laser effect in regeneration of skeletal muscle in mice. *Lasers in Medical Science* 2001;**16**:44–51.

Andersson 1999

Andersson G, Lyttkens L. A meta-analytic review of psychological treatments for tinnitus. *British Journal of Audiology* 1999;**33**(4):201–10.

Argstatter 2008

Argstatter H, Krick C, Bolay HV. Music therapy in chronic tonal tinnitus. Heidelberg model of evidence-based music therapy. *HNO* 2008;**56**(7):678–85.

ATA 2004

American Tinnitus Association. <http://www.ata.org> 2004.

Axelsson 1985

Axelsson A, Sandh A. Tinnitus in noise-induced hearing loss. *British Journal of Audiology* 1985;**19**(4):271–6.

Baguley 1992

Baguley DM, Moffat DA, Hardy DG. What is the effect of translabyrinthine acoustic schwannoma removal upon tinnitus?. *Journal of Laryngology and Otolaryngology* 1992;**106**: 329–31.

Baldo 2006

Baldo P, Doree C, Lazzarini R, Molin P, McFerran DJ. Antidepressants for patients with tinnitus. *Cochrane Database of Systematic Reviews* 2006, Issue 4. [DOI: 10.1002/14651858.CD003853.pub2]

Basford 1995

Basford JR. Low intensity laser therapy: still not an established clinical tool. *Lasers in Surgery and Medicine* 1995;**16**(4):331–42.

Becher 1996

Becher S, Struwe F, Schwenzer C, Weber K. Risk of hearing loss caused by high volume music - presenting an educational concept for preventing hearing loss in adolescents. *Gesundheitswesen* 1996;**58**(2):91–5.

Belkin 1994

Belkin M, Schwartz M. Evidence for the existence of low-energy laser bioeffects on the nervous system. *Neurosurgical Review* 1994;**17**:7–17.

Bennett 2007

Bennett MH, Kertesz T, Yeung P. Hyperbaric oxygen for idiopathic sudden sensorineural hearing loss and tinnitus. *Cochrane Database of Systematic Reviews* 2007, Issue 1. [DOI: 10.1002/14651858.CD004739.pub3]

Bjordan 2007

Bjordan J, Johnson MI, Lopes-Martins RA, Bogen B, Chow R, Ljunggren AE. Short-term efficacy of physical interventions in osteoarthritic knee pain. A systematic review and meta-analysis of randomised placebo-controlled trials. *BMC Musculoskeletal Disorders* 2007;**8**:51.

Bjordan 2008

Bjordan JM, Lopes-Martins RA, Joensen J, Couppe C, Ljunggren AE, Stergioulas A, et al. A systematic review with procedural assessments and meta-analysis of low level laser therapy in lateral elbow tendinopathy (tennis elbow). *BMC Musculoskeletal Disorders* 2008;**9**:75.

Briner 1995

Briner W. A behavioural nosology for tinnitus. *Psychological Reports* 1995;**77**(1):27–34.

Brummett 1980

Brummett RE. Drug-induced ototoxicity. *Drugs* 1980;**19**(6):412–28.

Budd 1995

Budd RJ, Pugh R. The relationship between locus of control, tinnitus severity, and emotional distress in a group of tinnitus sufferers. *Journal of Psychosomatic Research* 1995;**39**:1015–8.

Chouard 2001

Chouard CH. Urban noise pollution. *Comptes Rendus de l'Académie des Sciences. Série III, Sciences de la vie* 2001;**324**(7):657–61.

Christiansson 1993

Christiansson BA, Wintzell KA. An audiological survey of officers at an infantry regiment. *Scandinavian Audiology* 1993;**22**(3):147–52.

Chung 1980

Chung DY, Gannon RP. Hearing loss due to noise trauma. *Journal of Laryngology and Otolaryngology* 1980;**9**(4):419–23.

Daniell 1998

Daniell WE, Fulton-Kehoe D, Smith-Weller T, Franklin GM. Occupational hearing loss in Washington state, 1984–1991: II. Morbidity and associated costs. *American Journal of Industrial Medicine* 1998;**33**(6):529–36.

Dauman 1992

Dauman R, Tyler RS. Some considerations on the classification of tinnitus. Proceedings of the Fourth International Tinnitus Seminar, Bordeaux. 1992:225–9.

Davis 2000

Davis A, El Rafaie A. Epidemiology of tinnitus. In: Richard Tyler editor(s). *Tinnitus Handbook*. San Diego: Singular Publishing Group, 2000.

Enwemeka 2004

Enwemeka CS, Parker JC, Dowdy DC, Harkness EE, Sanford LE, Woodruff LD. The efficacy of low-power lasers in tissue repair and pain control: a meta-analysis study. *Photomedicine and Laser Surgery* 2004;**22**:323–9.

Erlandsson 1992

Erlandsson SI, Hallberg LRM, Axelsson A. Psychological and audiological correlates of perceived tinnitus severity. *Audiology* 1992;**31**:168–79.

Ernst 1999

Ernst E, Stevinson C. Ginkgo biloba for tinnitus: a review. *Clinical Otolaryngology* 1999;**24**:164–7.

Fleischer 1999

Fleischer G, Hoffmann E, Lang R, Muller R. Documentation of the effects of child cap pistols. *HNO* 1999;**47**(6):535–40.

Griest 1998

Griest SE, Bishop PM. Tinnitus as an early indicator of permanent hearing loss. A 15 year longitudinal study of noise exposed workers. *AAOHN Journal: Official Journal of the American Association of Occupational Health Nurses* 1998;**46**(7):325–9.

Gungor 2008

Gungor A, Dogru S, Cincik H, Erkul E, Poyrazoglu E. Effectiveness of transmeatal low power laser irradiation for chronic tinnitus. *Journal of Laryngology and Otolaryngology* 2008; **122**(5):447–51.

Hahn 2001

Hahn A, Sejna I, Stolbova K, Cocek A. Combined laser-Egb 761 tinnitus therapy. *Acta Oto-Laryngologica. Supplement* 2001;**545**:92–3.

Halford 1991

Halford JBS, Anderson SD. Tinnitus severity measured by a subjective scale, audiometry and clinical judgement. *Journal of Laryngology and Otolaryngology* 1991;**105**:89–93.

Hallam 1996

Hallam RS. *Manual of the Tinnitus Questionnaire*. London: The Psychological Corporation, 1996.

Handbook 2011

Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hashmi 2010

Hashmi JT, Huang YY, Osmani BZ, Sharma SK, Naeser MA, Hamblin MR. Role of low-level laser therapy in neurorehabilitation. *PM & R: The Journal of Injury, Function, and Rehabilitation* 2010;**2**(12 Suppl 2):S292–305.

Heller 1953

Heller MF, Bergman M. Tinnitus aurium in normally hearing persons. *Annals of Otolaryngology, Rhinology and Laryngology* 1953;**62**:73–83.

Henry 1995

Henry JL, Wilson PH. Coping with tinnitus: two studies of psychological and audiological characteristics of patients with high and low tinnitus-related distress. *International Tinnitus Journal* 1995;**1**:85–92.

Hilton 2004

Hilton MP, Stuart EL. Ginkgo biloba for tinnitus. *Cochrane Database of Systematic Reviews* 2004, Issue 2. [DOI: 10.1002/14651858.CD003852.pub2]

Hobson 2010

Hobson J, Chisholm E, Loveland M. Sound therapy (masking) in the management of tinnitus in adults. *Cochrane Database of Systematic Reviews* 2010, Issue 12. [DOI: 10.1002/14651858.CD006371.pub2]

Hoekstra 2011

Hoekstra CEL, Rynja SP, van Zanten GA, Rovers M. Anticonvulsants for tinnitus. *Cochrane Database of Systematic Reviews* 2011, Issue 7. [DOI: 10.1002/14651858.CD007960.pub2]

Holger 1994

Holger KM, Axelsson A, Pringle I. Ginkgo biloba extract for the treatment of tinnitus. *Audiology* 1994;**33**:85–92.

Jastreboff 1990

Jastreboff PJ. Phantom auditory perception (tinnitus): mechanisms of generation and perception. *Neuroscience Research* 1990;**8**:221–54.

Jastreboff 2004

Jastreboff PJ, Hazell JWP. *Tinnitus Retraining Therapy. Implementing the Neurophysiological Model*. Cambridge: Cambridge University Press, 2004.

Karu 1986

Karu TI. Molecular mechanism of the therapeutic effect of low-intensity laser irradiation. *Doklady Akademii Nauk SSSR* 1986;**291**(5):1245–9.

Karu 1989

Karu T. Photobiology of low-power laser effects. *Health Physics* 1989;**56**(5):691–704.

Karu 1995

Karu T, Pyatibrat L, Kalendo G. Irradiation with He-Ne laser increases ATP level in cells cultivated in vitro. *Journal of Photochemistry and Photobiology. B, Biology* 1995;**27**(3): 219–23.

Kaviani 2011

Kaviani A, Djavid GE, Ataie-Fashtami L, Fateh M, Ghodsi M, Salami M, et al. A randomized clinical trial on the effect of low-level laser therapy on chronic diabetic foot wound healing: a preliminary report. *Photomedicine and Laser Surgery* 2011;**29**(2):109–14.

Kipshidze 2001

Kipshidze N, Nikolaychik V, Keelan MH, Shankar LR, Khanna A, Kornowski R, et al. Low-power helium: neon laser irradiation enhances production of vascular endothelial growth factor and promotes growth of endothelial cells in vitro. *Lasers in Surgery and Medicine* 2001;**28**(4):355–64.

Koester 2004

Koester M, Storck C, Zorowka P. Tinnitus - classification, causes, diagnosis, treatment and prognosis. *MMW Fortschritte der Medizin* 2004;**146**(1-2):23–4, 26–8; quiz 29–30.

Kowalska 2001

Kowalska S, Sulkowski W. Tinnitus in noise-induced hearing impairment. *Medycyna Pracy* 2001;**52**(5):305–13.

Kuk 1990

Kuk FK, Tyler RS, Russell D, Jordan H. The psychometric properties of a tinnitus handicap questionnaire. *Ear and Hearing* 1990;**11**:434–45.

Lee 1999

Lee LT. A study of the noise hazard to employees in local discotheques. *Singapore Medical Journal* 1999;**40**(9):571–4.

Li 2009

Li Y, Zeng RF, Zheng D. Acupuncture for tinnitus. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD008149]

Lockwood 1999

Lockwood AH, Alvi RJ, Burkard RF, Galantowicz PJ, Coad ML, Wack DS. Neuroanatomy of tinnitus. *Scandinavian Audiology Supplementum* 1999;**51**:47–52.

Luxon 1993

Luxon LM. Tinnitus: its causes, diagnosis and treatment. *BMJ* 1993;**306**:1490–1.

Martinez-Devesa 2010

Martinez-Devesa P, Waddell A, Perera R, Theodoulou M. Cognitive behavioural therapy for tinnitus. *Cochrane Database of Systematic Reviews* 2010, Issue 9. [DOI: 10.1002/14651858.CD005233.pub3]

Marx 1999

Marx SV, Langman AW, Crane RC. Accuracy of the fast spin echo magnetic resonance imaging in the diagnosis of vestibular schwannoma. *American Journal of Otolaryngology* 1999;**20**(4):211–6.

Mazurek 2007

Mazurek B, Stöver T, Haupt H, Gross J, Szczepek A. The role of cochlear neurotransmitters in tinnitus. *HNO* 2007;**55**(12):964–71.

McCombe 2001

McCombe A, Baguley D, Coles R, McKenna L, McKinney C, Windle-Taylor P. Guidelines for the grading of tinnitus severity: the results of a working group commissioned by the British Association of Otolaryngologists - Head and Neck Surgeons. *Clinical Otolaryngology* 2001;**26**:388–93.

McShane 1988

McShane DP, Hyde ML, Alberti PW. Tinnitus prevalence in industrial hearing loss compensation claimants. *Clinical Otolaryngology* 1988;**13**(5):323–30.

Melinek 1976

Melinek M, Naggan L, Altman M. Acute acoustic trauma - a clinical investigation and prognosis in 433 symptomatic soldiers. *Israel Journal of Medical Sciences* 1976;**12**(6):590–9.

Meng 2011

Meng Z, Liu S, Zheng Y. Repetitive transcranial magnetic stimulation for tinnitus. *Cochrane Database of Systematic Reviews* 2011, Issue 10. [DOI: 10.1002/14651858.CD007946.pub2]

Mester 1972

Mester E, Szende B, Spiry T, Scher A. Stimulation of wound healing by laser rays. *Acta Chirurgica Academiae Scientiarum Hungaricae* 1972;**13**(3):315–24.

Metternich 1999

Metternich FU, Brusis T. Acute hearing loss and tinnitus caused by amplified recreational music. *Laryngorhinootologie* 1999;**78**(11):614–9.

Mirz 1999

Mirz F, Zachariae R, Andersen SE, Nielsen AG, Johansen LV, Bjerring P. The low-power laser in the treatment of tinnitus. *Clinical Otolaryngology and Allied Sciences* 1999;**24**(4):346–54.

Mrena 2002

Mrena R, Savolainen S, Kuokkanen JT, Ylikoski J. Characteristics of tinnitus induced by acute acoustic trauma: a long-term follow-up. *Audiology and Neuro-otology* 2002;**7**(2):122–30.

Nakashima 2002

Nakashima T, Ueda H, Misawa H, Suzuki T, Tominaga M, Ito A, et al. Transmeatal low-power laser irradiation for tinnitus. *Otology and Neurotology* 2002;**23**(3):296–300.

Neuberger 1992

Neuberger M, Korpert K, Raber A, Schwetz F, Bauer P. Hearing loss from industrial noise, head injury and ear disease. A multivariate analysis on audiometric examinations of 110,647 workers. *Audiology* 1992;**31**(1):45–57.

Newman 1996

Newman C, Jacobson G, Spitzer B. Development of the tinnitus handicap inventory. *Archives of Otolaryngology - Head & Neck Surgery* 1996;**122**:143–7.

Olszewski 2008

Olszewski J, Kowalska S, Kuś mierzcyk K. Tinnitus diagnosis and treatment on the basis of our experiences. *Otolaryngologia Polska* 2008;**62**(1):76–81.

Oregon 1995

Oregon Tinnitus Archive. <http://www.tinnitusarchive.org/> 1995.

Oron 2007

Oron U, Ilie S, De Taboada L, Streeter J. Ga-As (808nm) laser irradiation enhances ATP production in human neuronal cells in culture. *Photomedicine and Laser Surgery* 2007;**25**(3):180–2.

Passarella 1984

Passarella S, Casamassima E, Molinari S, Pastore D, Quagliariello E, Catalano IM, et al. Increase of proton electrochemical potential and ATP synthesis in rat liver mitochondria irradiated in vitro by helium-neon laser. *FEBS Letters* 1984;**175**(1):95–9.

Phillips 2010

Phillips JS, McFerran D. Tinnitus Retraining Therapy (TRT) for tinnitus. *Cochrane Database of Systematic Reviews* 2010, Issue 3. [DOI: 10.1002/14651858.CD007330.pub2]

Phoon 1993

Phoon WH, Lee HS, Chia SE. Tinnitus in noise-exposed workers. *Occupational Medicine* 1993;**43**(1):35–8.

Plath 1995

Plath P, Olivier J. Results of combined low-power laser therapy and extracts of Ginkgo biloba in causes of sensorineural hearing loss and tinnitus. *Advances in Otorhino-laryngology* 1995;**49**:101–4.

Reddy 1998

Reddy GK, Stehno-Bittel L, Enwemeka CS. Laser photostimulation of collagen production in healing rabbit Achilles tendons. *Lasers in Surgery and Medicine* 1998;**22**(5):281–7.

Rejali 2004

Rejali D, Sivakumar A, Balaji N. Ginkgo biloba does not benefit patients with tinnitus: a randomized placebo-controlled double-blind trial and meta-analysis of randomized trials. *Clinical Otolaryngology* 2004;**29**(3):226–31.

RevMan 2011

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.

Rhee 2011

Rhee CK, He P, Jung JY, Ahn JC, Chung PS, Suh MW. Effect of low-level laser therapy on cochlear hair cell recovery after gentamicin-induced ototoxicity. *Lasers in Medical Science* 2011;**4**: [Epub ahead of print].

Robinson 2007

Robinson S. Antidepressants for treatment of tinnitus. *Progress in Brain Research* 2007;**166**:263–71.

Rochkind 1987

Rochkind S, Barrnea L, Razon N, Bartal A, Schwartz M. Stimulatory effect of He-Ne low dose laser on injured sciatic nerves of rats. *Neurosurgery* 1987;**20**:843–47.

Rochkind 1992

Rochkind S, Ouaknine GE. New trend in neuroscience: low power laser effect on peripheral and central nervous system (basic science, preclinical, and clinical studies). *Neurological Research* 1992;**11**:2–11.

Saayman 2011

Saayman L, Hay C, Abrahames H. Chiropractic manipulative therapy and low-level laser therapy in the management of cervical facet dysfunction: a randomized controlled study. *Journal of Manipulative and Physiological Therapeutics* 2011;**34**(3):153–63.

Saunders 1998

Saunders JE, Slattery WH, Luxford WM. Automobile airbag impulse noise: otologic symptoms in six patients. *Otolaryngology - Head and Neck Surgery* 1998;**118**(2):228–34.

Seidman 1998

Seidman MD. Glutamate antagonists, steroids and antioxidants as therapeutic options for hearing loss and

tinnitus and the use of an inner ear drug delivery system. *International Tinnitus Journal* 1998;**4**(2):148–54.

Shea 1981

Shea A. Otosclerosis and tinnitus. *Journal of Laryngology and Otology Supplement* 1981;**4**:149–50.

Shiomi 1997

Shiomi Y, Takahashi H, Honjo I, Kojima H, Naito Y, Fujiki N. Efficacy of transmeatal low power laser irradiation on tinnitus: a preliminary report. *Auris Nasus Larynx* 1997;**24**(1):39–42.

Siedentopf 2007

Siedentopf CM, Ischebeck A, Haala IA, Mottaghy FM, Schikora D, Verius M, et al. Neural correlates of transmeatal cochlear laser (TCL) stimulation in healthy human subjects. *Neuroscience Letters* 2007;**411**(3):189–93.

Siendentopf 2002

Siendentopf C, Golaszewski SM, Mottaghy FM, Ru ff CC, Felber S, Schlager A. Functional magnetic resonance imaging detects activation of the visual association cortex during laser acupuncture of the foot in humans. *Neuroscience Letters* 2002;**327**:3–56.

Silva 2011

Silva GB, Mendonça EF, Bariani C, Antunes HS, Silva MA. The prevention of induced oral mucositis with low-level laser therapy in bone marrow transplantation patients: a randomized clinical trial. *Photomedicine and Laser Surgery* 2011;**29**(1):27–31.

Sindhusake 2003

Sindhusake D, Mitchell P, Newall P, Golding M, Roachtchina E, Rubin G. Prevalence and characteristics of tinnitus in older adults: the Blue Mountains Hearing Study. *International Journal of Audiology* 2003;**42**(5):289–94.

Stephens 1991

Stephens D, Hetu R. Impairment, disability and handicap in audiology: towards a consensus. *Audiology* 1991;**20**:185–200.

Sullivan 1989

Sullivan MD, Dobie RA, Saki CS, Katon WJ. Treatment of depressed tinnitus patients with nortriptyline. *Annals of Otolaryngology and Laryngology* 1989;**98**(11):867–72.

Sullivan 1992

Sullivan M, Katon WJ, Russo J, Dobie R, Saki C. Somatization, comorbidity, and the quality of life: measuring the effect of depression upon chronic mental illness. *Psychiatric Medicine* 1992;**10**:61–76.

Sullivan 1993

Sullivan M, Katon W, Russo J, Dobie R, Sakai C. A randomized trial of nortriptyline for severe chronic tinnitus. *Archives of Internal Medicine* 1993;**153**:2251–9.

Sullivan 1994

Sullivan M, Katon W, Russo J, Dobie R, Sakai C. Coping and marital support as correlates of tinnitus disability. *General Hospital Psychiatry* 1994;**16**:259–66.

Sweetow 1990

Sweetow RW, Levy MC. Tinnitus severity scaling for diagnostic/therapeutic usage. *Hearing Instruments* 1990;**41**(20-1):46.

Szundi 2001

Szundi I, Liao GL, Einarsdóttir O. Near-infrared time-resolved optical absorption studies of the reaction of fully reduced cytochrome c oxidase with dioxygen. *Biochemistry* 2001;**40**(8):2332–9.

Tauber 2003

Tauber S, Schorn K, Beyer W, Baumgartner R. Transmeatal cochlear laser (TCL) treatment of cochlear dysfunction: a feasibility study for chronic tinnitus. *Lasers in Medical Science* 2003;**18**(3):154–61.

Teggi 2009

Teggi R, Bellini C, Piccioni L, Palonta F, Bussi M. Transmeatal low-level laser therapy for chronic tinnitus with cochlear dysfunction. *Audiology and Neuro-Otology* 2009;**14**(2):115–20.

Temmel 1999

Temmel AF, Kierner AC, Steurer M, Riedl S, Innitzer J. Hearing loss and tinnitus in acute acoustic trauma. *Wiener Klinische Wochenschrift* 1999;**111**(21):891–3.

Tunér 1999

Tunér J, Hode L (eds). *Low level laser therapy - clinical practice and scientific background*. Grängesberg, Sweden: Prima Books AB, 1999.

van Breugel 1992

van Breugel HH, Bär PR. Power density and exposure time of He-Ne laser irradiation are more important than total energy dose in photobiomodulation of human fibroblast in vitro. *Lasers in Surgery and Medicine* 1992;**12**(5):528–37.

Weissman 2000

Weissman JL, Hirsch BE. Imaging of tinnitus: a review. *Radiology* 2000;**216**(2):342–9.

Wenzel 2004

Wenzel GI, Pikkula B, Choi CH, Anvari B, Oghalai JS. Laser irradiation of the guinea pig basilar membrane. *Lasers in Surgery and Medicine* 2004;**35**(3):174–80.

Wenzel 2007

Wenzel GI, Anvari B, Mazhar A, Pikkula B, Oghalai JS. Laser-induced collagen remodeling and deposition within the basilar membrane of the mouse cochlea. *Journal of Biomedical Optics* 2007;**12**(2):021007.

Wilden 1996

Wilden L, Dindinger D. Treatment of chronic diseases of the inner ear with low level laser therapy (LLLT): pilot project. *Laser Therapy* 1996;**8**:209–12.

Wilson 1998

Wilson PH, Henry JL. Development and psychometric properties of a measure of dysfunctional cognitions associated with tinnitus. *International Tinnitus Journal* 1998;**4**(1):23–30.

Woodruff 2004

Woodruff LD, Bounkeo JM, Brannon WM, Dawes KS, Barham CD, Waddell DL, et al. The efficacy of laser therapy in wound repair: a meta-analysis of the literature. *Photomedicine and Laser Surgery* 2004;**22**(3):241–7.

Yazdani 2012

Yazdani SO, Golestaneh AF, Shafiee A, Hafizi M, Omrani HA, Soleimani M. Effects of low level laser therapy on proliferation and neurotrophic factor gene expression of human schwann cells in vitro. *Journal of Photochemistry and Photobiology. B, Biology* 2012;**6**(107):9–13.

Yu 1994

Yu W, Naim J, Lanzafame RJ. The effects of photoradiation on the secretion of TGF- β , PDGF and bFGF from fibroblasts in vitro. *Photochemistry and Photobiology* 1994;**59**:167–70.

* Indicates the major publication for the study

ADDITIONAL TABLES**Table 1. Tinnitus questionnaires**

Title	No. of items/factors	Psychometrics
Tinnitus Questionnaire (Hallam 1996)	52 items, 5 factors	$\alpha = 0.91$ for total scale; for subscales $\alpha = 0.76$ to $\alpha = 0.94$
Tinnitus Handicap Questionnaire (Kuk 1990)	27 items, 3 factors	$\alpha = 0.93$ for total scale
Tinnitus Severity Scale (Sweetow 1990)	15 items	Alpha not reported
Subjective Tinnitus Severity Scale (Halford 1991)	16 items	$\alpha = 0.84$

Table 1. Tinnitus questionnaires (Continued)

Tinnitus Handicap/Support Scale (Erlandsson 1992)	28 items, 3 factors	Alpha not reported
Tinnitus Handicap Inventory (Newman 1996)	25 items, 3 scales	a = 0.93 for total scale
Tinnitus coping strategy questionnaire (Henry 1995)	33	a = 0.88
Tinnitus coping style questionnaire (Budd 1995)	40	-
Tinnitus cognitions questionnaire (Wilson 1998)	-	-

APPENDICES

Appendix I. CENTRAL search strategy

- #1 MeSH descriptor Tinnitus explode all trees
- #2 tinnit*
- #3 (#1 OR #2)
- #4 MeSH descriptor Laser Therapy explode all trees
- #5 MeSH descriptor Lasers explode all trees
- #6 laser* OR lllt
- #7 #4 OR #5 OR #6
- #8 #3 AND #7

HISTORY

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CONTRIBUTIONS OF AUTHORS

Zhe Peng: lead author, searching, selection of studies, data extraction, drafting and co-drafting of the protocol/review, assistance with statistics, data analysis and data presentation, update of the review.

Xiu-Qi Chen: selection of studies, data extraction, assistance with statistics, data analysis, update of the review.

Shu-Sheng Gong: selection of studies, assistance with statistics.

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DECLARATIONS OF INTEREST

None known.

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