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The effect of photobiomodulation on tinnitus: a systematic review

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Review Article

Manohar Bance takes responsibility for the integrity of the content of the paper

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Abstract

Objective. To establish outcomes following photobiomodulation therapy for tinnitus in humans and animal studies.
Methods. A systematic review and narrative synthesis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. The databases searched were: Medline, Embase, Cochrane Central Register of Controlled Trials ('Central'), ClinicalTrials.gov and Web of Science including the Web of Science Core collection. There were no limits on language or year of publication.
Results. The searches identified 194 abstracts and 61 full texts. Twenty-eight studies met the inclusion criteria, reporting outcomes in 1483 humans (26 studies) and 34 animals (2 studies). Photobiomodulation therapy parameters included 10 different wavelengths, and duration ranged from 9 seconds to 30 minutes per session. Follow up ranged from 7 days to 6 months.
Conclusion. Tinnitus outcomes following photobiomodulation therapy are generally positive and superior to no photobiomodulation therapy; however, evidence of long-term therapeutic benefit is deficient. Photobiomodulation therapy enables concentrated, focused delivery of light therapy to the inner ear through a non-invasive manner, with minimal side effects.

Introduction

Background and epidemiology

Tinnitus can be defined as the perception of sounds without an external source.[1] It can be classified into objective and subjective types. Subjective tinnitus is more common and not audible to the observer, usually arising from neuropsychological problems. Objective tinnitus is defined as tinnitus that is audible to another person as a sound emanating from the ear canal.[2] The British Tinnitus Association state that around one in eight people live with persistent tinnitus in the UK.[3] Tinnitus impairs daily life activities for 3–5 per cent of individuals, causing complications such as sleep deprivation, anxiety and depression.[4] There are a wide range of causes, but given the limited knowledge of its physiology, it remains an obscure symptom with limited treatment success.

It is estimated that 1.05 million primary care consultations take place every year in the UK regarding tinnitus, with the treatment pathway for tinnitus costing the National Health Service £750 million annually.[3] Treatment for tinnitus is limited, and largely dependent upon the underlying cause. Currently, there are no curative pharmacological therapies, with such approaches often limited to addressing anxiety and depression associated with tinnitus. Whilst pharmacotherapy is not a mainstay of treatment, several agents have been used, typically without a strong evidence base. Such drugs include sedatives, anticonvulsants, antidepressants, local anaesthetics, antihistamines, antipsychotics and botulinum toxin A.[5] Such treatment options provide mixed or inconsistent benefits for tinnitus. Non-pharmacological and surgical approaches have been used in selected cases; these modalities have not shown dramatic therapeutic effects.[6,7]

Photobiomodulation therapy

Photobiomodulation therapy could provide an alternative treatment for patients with chronic tinnitus. Photobiomodulation therapy utilises light energy to enhance or modulate the activities of specific organs, in order to improve or change the function of body tissues. It is a non-invasive therapy used in several medical specialties, particularly in

dermatology and neurology, to treat skin lesions and neurodegenerative disorders respectively.[8] Photobiomodulation therapy has been shown to reduce pain and trigger the regeneration of nerves and other tissues.

The mechanism of photobiomodulation therapy on neural cell recovery and regeneration is yet to be fully understood. The prevailing theory focuses on mitochondrial cytochrome c oxidase, a key protein in cellular metabolism and repair, and one of three major proteins in the human body responding to near-infrared wavelength.[9] These proteins absorb near-infrared wavelength energy and then modulate biochemical reactions within cells. Cytochrome c oxidase is a large transmembrane protein complex in the mitochondrial electron transport chain that consists of five protein complexes which together produce adenosine triphosphate (ATP).[10] This theory is further supported by research showing that photobiomodulation therapy enhances ATP production.[11] Increased ATP production may lead to enhanced cell metabolism, promoting the damage–repair process.

Transmeatal cochlear low-level laser irradiation, also known as photobiomodulation therapy, has been introduced as an alternative modality for cochlear dysfunction such as chronic cochlear tinnitus. Clinically, lasers have been used since the 1990s to treat tinnitus.[12] However, the therapeutic benefit remains uncertain, with several studies demonstrating no significant improvement in tinnitus symptoms with photobiomodulation therapy.[13,14] To the best of the authors' knowledge, the efficacy of photobiomodulation therapy use in the management of tinnitus has only been systematically reviewed once previously, with the exclusion of non-randomised controlled trials and non-human trials.[15] The current study aimed to systematically review all study types assessing the use of photobiomodulation therapy to treat tinnitus to date.

Objectives

This review aimed to assess if the application of photobiomodulation therapy is effective for the treatment of tinnitus, analysing both animal and human study evidence.

Materials and methods

The study protocol was registered in the International Prospective Register of Systematic Reviews ('PROSPERO') (registration number: CRD42020212259), and was created according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses ('PRISMA') guidelines.[16]

Population, inclusion, comparator, outcomes

The population, inclusion, comparator, outcomes ('PICO') framework was used to facilitate the literature review. In this instance, the populations are humans or animals, and the intervention is photobiomodulation therapy. There is no formal comparator or control. The comparators are expected to vary according to the study type. Comparators may include other methods of tinnitus symptom control; for example, the administration of drugs via systemic or local routes. The primary outcomes are pre- and post-photobiomodulation therapy tinnitus outcomes. These include: tinnitus visual analogue scales (VASs), the Tinnitus Handicap Inventory, loudness matching of tinnitus, the Persian Tinnitus Questionnaire, a vertigo assessment, the Tinnitus Severity Index and a subjective tinnitus analysis. The secondary outcomes are: general well-being, audiological outcomes, complications, adverse events and side effects associated with photobiomodulation therapy.

Study inclusion criteria

All experimental study designs were eligible for inclusion, including case–control, case series, cohort, randomised controlled trials and animal studies (live, explant and *in vitro*). Opinion pieces were not included in this review. Animal studies of photobiomodulation therapy for tinnitus were required to include at least one quantitative outcome measure. There were no restrictions placed on the follow-up length or the duration of the study. Only studies with the full text available were included. Exclusion criteria included studies with insufficient data and those that did not assess the effect of photobiomodulation therapy on tinnitus outcomes.

Search strategy

The following electronic databases were searched: Medline, Embase, Cochrane Central Register of Controlled Trials ('Central'), ClinicalTrials.gov, Web of Science, Biosis, Data Citation Index, Derwent Innovations Index, KCI Korean Journal Database, Medline, Russian Citation Index, Scientific Electronic Library Online ('SciELO') Citation index and Zoological Records. No limit was placed on language or year of publication. A search was conducted using Medical Subject Headings and the Boolean search technique for 'tinnitus' and 'photobiomodulation'.

The search strategy for the Embase database is presented in Table 1; modified versions of this search strategy were used for other electronic databases (Appendix 1). Manual searches of the reference lists of the included and relevant systematic reviews and a citation search were conducted to identify additional studies missed from the electronic database searches.

Selection of studies

Searches were performed on 20 December 2020 by one author (YN) and checked by a second author (NZ). Two reviewers (YN and NZ) independently screened titles and abstracts of the studies from the database search for duplicates and inclusion. Full texts were reviewed by two authors (YN and NZ)

Table 1. Search strategy for Embase database

1	Tinnitus
2	Ringing
3	Menieres
4	1 OR 2 OR 3
5	Photobiomodulation
6	Photobiomodulation therapy
7	PBM
8	PBMT
9	Low Level Laser therapy
10	LLLT
11	Near infrared light
12	5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11
13	4 AND 12

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independently against the inclusion and exclusion criteria. Disagreements at the abstract and full-text screening stages were discussed within the author team (YN and NZ) and, where applicable, with a third reviewer (JM), whereupon consensus was reached in determining eligible studies for inclusion. In the same manner, a secondary search was conducted on 21 November 2022 by two authors (AL and JD-M), to ensure all eligible studies were included at the time of publication, and corroborated by a third author (JM).

Data extraction

A standardised form using Microsoft Excel® software was used for data extraction from the included studies. This was designed and piloted prior to the data extraction phase. Data were extracted by the first reviewer (YN) and then checked by second reviewer (NZ). The data of interest were: study characteristics (study design, location and duration), primary and secondary outcome data, and adverse events. Missing data were sought, where possible, by email contact with study authors. Any discrepancies were identified and resolved through discussion within the author team. This process was followed for the secondary search conducted by two authors (AL and JD-M).

Risk of bias quality assessment

Two review authors (YN and NZ) independently assessed the methodological quality of the included studies. Animal studies were assessed using the Systematic Review Centre for Laboratory Animal Experimentation ('SYRCLE') tool.[17] Human studies were assessed using the Oxford Centre for Evidence Based Medicine grading system, the Cochrane Risk of Bias 2 tool for randomised trials ('RoB 2') and the Brazzelli risk of bias tool for non-randomised studies.[18–20] Any disagreements were resolved through discussion between two authors (YN and NZ), and, where necessary, via consultation with the third review author (JM). The above process was repeated for the secondary search, conducted by two authors (AL and JD-M).

Results

A flow sheet detailing study selection according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, based on initial searches, is included in Figure 1. Given the heterogeneity of sampling, reporting, treatment and outcome measures, a meta-analysis was not performed.

Description of studies

Twenty-eight studies met the inclusion criteria, with a total of 1517 subjects (1483 humans in 26 studies, and 34 animals in 2 studies).[12–14,21–44] At least 916 subjects underwent photobiomodulation therapy intervention. One study reported two trial outcomes for both human and animal subjects;[21] this review has reported these trial outcomes as two separate studies throughout.

Twenty-six studies assessed the effect of photobiomodulation therapy on humans with tinnitus; these were published between 1995 and 2022.[12–14,21–43] Among these, 18 were randomised controlled trials (including 1 pilot study), 5 were cohort studies, 2 were case series and 1 was a self-controlled clinical study. The type of photobiomodulation therapy used

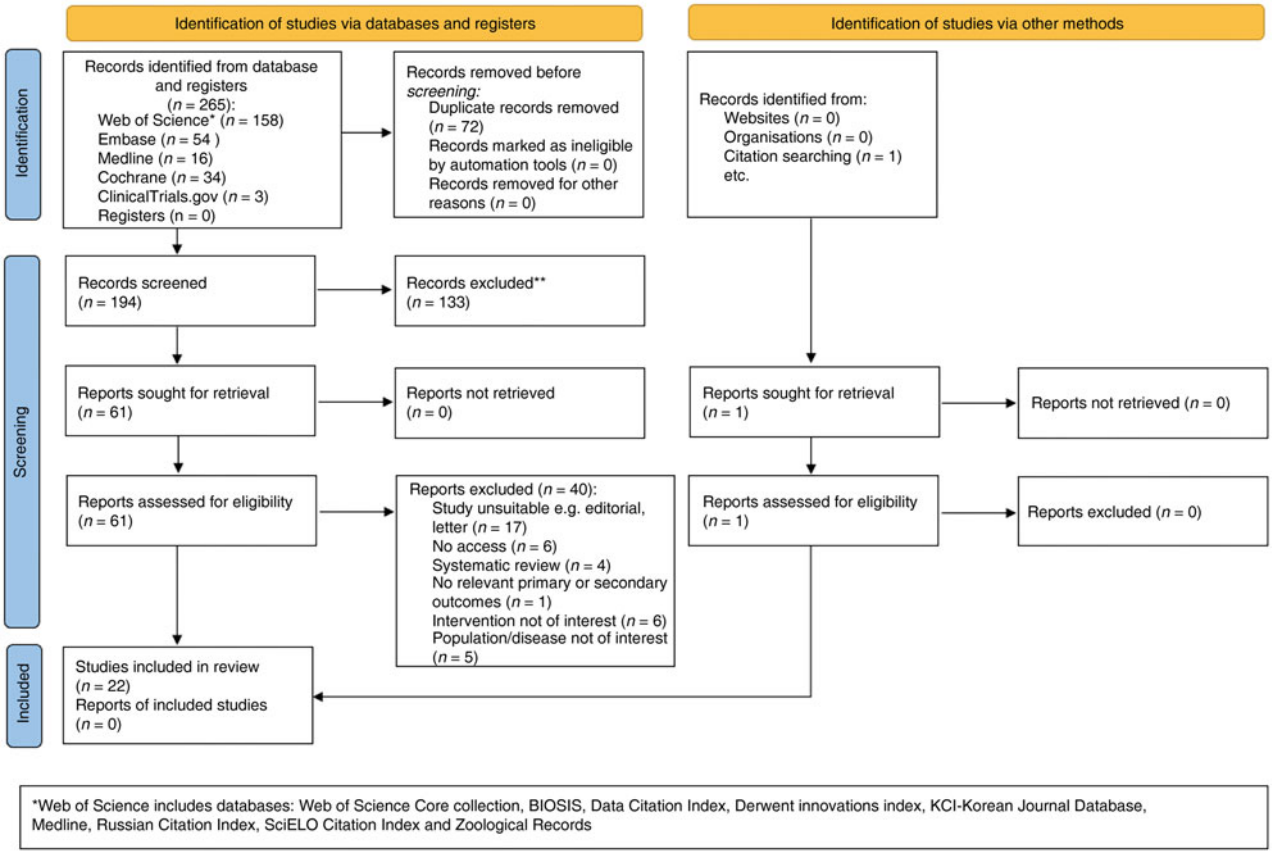

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses ('PRISMA') flow diagram.

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was described in detail in all studies. The wavelength used was classified in all studies: 12 used 650 nm, 4 used 840 nm, 2 used 810 nm, 2 used 904 nm, 1 used 830 nm, 1 used 808 nm, 1 used 808 nm and 630 nm, 1 used 808 nm and 660 nm, 1 used 830 nm and 632.8 nm, and 1 used 635 nm or 830 nm. The duration of photobiomodulation therapy ranged from 7 days to 6 months, and the application time per session ranged from 9 seconds to 30 minutes.

Two studies were conducted on animal models, published in 2006 and 2013, with the former dually reporting on human subjects as a separate study.[21,22] Rhee *et al.* reported a randomised controlled trial. Park *et al.* used rat models, whilst Rhee *et al.* used guinea pig models. The type of photobiomodulation therapy was described in detail in both studies. The wavelength used was 830 nm for a duration of 30 minutes per session in both. The follow-up duration was not stated by Rhee *et al.* and was 24 hours post treatment in the study by Park *et al.*[21,22] Study characteristics for the human and animal studies included in this review are summarised in Table 2.[12–14,21–44]

Quality of studies

Included studies mainly consisted of human randomised controlled trials (18 of 28 studies). All included studies were prospective.

The 26 human studies had a minimum of 10 subjects who underwent photobiomodulation therapy. The studies included were Oxford Centre for Evidence Based Medicine grade I (n = 19), grade II (n = 6) and grade III (n = 1). All animal studies (n = 2) had a minimum of seven animals that underwent photobiomodulation therapy.

The heterogeneity of tinnitus outcome measures, photobiomodulation therapy duration, power and wavelength outcomes, within and between human and animal studies, precluded a meta-analysis. Within the human studies, the limitations were: reporting of adverse events following photobiomodulation therapy, average age of subjects, and values of the pre-photobiomodulation therapy assessment. Quality assessment of the human studies is summarised in Figures 2 and 3. Within the animal studies, there were limitations in: post-treatment observation duration of animals receiving photobiomodulation therapy, tinnitus data prior to photobiomodulation therapy delivery, and housing of animals. Quality assessment of animal studies is summarised in Figure 4.

Tinnitus outcomes

Tinnitus outcomes in humans are summarised in Table 3. A total of 11 different tinnitus outcome measures were used. There were inconsistencies regarding the use of pre- and post-photobiomodulation therapy across all included studies. All studies, except one,[26] reported that pre-photobiomodulation therapy tinnitus assessments were conducted. Tinnitus VASs were recorded in 17 studies, the Tinnitus Handicap Inventory in 12 studies, and audiological outcomes and subjective tinnitus analysis were reported in 7 studies respectively. Other post-photobiomodulation therapy outcome parameters included loudness matching of tinnitus, the Tinnitus Questionnaire, the Persian Tinnitus Questionnaire, general well-being assessment, vertigo assessment, the Tinnitus Severity Index and cervical range of motion (each reported in a single study). Whilst the cause of tinnitus was not always stated, tinnitus severity and type were recorded in all studies. Photobiomodulation therapy administration details were present in all studies, detailing the range of delivery and duration.

Tinnitus outcomes in animals are summarised in Table 4. A total of three different tinnitus outcomes measures were used. There were inconsistencies regarding the use of pre- and post-photobiomodulation therapy across the included studies. Only one study reported the values of the pre-photobiomodulation therapy tinnitus assessment. Gap pre-pulse inhibition of the acoustic startle reflex was recorded in one study before and after photobiomodulation therapy.[22] Values of gain in the slow harmonic acceleration rotation test and values of modulation in the off-vertical axis rotation test were measured in one study post-photobiomodulation therapy.[21]

Overall, there was a trend towards benefit from photobiomodulation therapy in both the animal and human studies, despite variations in parameters of delivery, wavelength, animal species or power used. Tinnitus outcomes improved in 20 of 26 human studies and 2 of 2 animal studies following photobiomodulation therapy, compared to no photobiomodulation therapy. One human study illustrated uncertain outcomes following photobiomodulation therapy for tinnitus, because of speculation regarding whether the placebo effect influenced the results.[13] Another human study demonstrated that the improvement in tinnitus outcomes following photobiomodulation therapy was not statistically significant, but hearing outcomes were statistically improved.[23] Moreover, five human studies found that photobiomodulation therapy improved tinnitus outcomes in the short term, but did not yield statistically significant results at follow up ranging between two weeks and three months.[14,24–27] However, four human studies did report sustained therapeutic benefit at follow up, which was demonstrated to be statistically significant (with follow up ranging between two and four weeks).[28–31] Three further studies reported statistically significant improvement immediately following treatment completion, but provided no follow-up data to demonstrate sustained benefit.[21,32,33] A further human study showed no objective improvement in transient evoked otoacoustic emissions measurement, but participants stated a subjective improvement in tinnitus.[34] Six studies reported no significant improvement in tinnitus with photobiomodulation therapy.[13,23,34–37] It is uncertain whether there is a relationship between longer duration of photobiomodulation therapy and greater improvement in tinnitus outcomes, given the heterogeneity of photobiomodulation therapy delivery, duration and outcomes assessment.

The wavelength and power used in the human studies were similar to those in the animal studies; however, animal studies comprised a shorter duration of administration and follow up when compared to human studies.[21,22] Reports of the assessment method used and the follow-up duration were heterogeneous across all human and animal studies.

Photobiomodulation therapy adverse events

None of the included studies reported on immediate adverse effects following photobiomodulation therapy administration. However, two studies reported side effects of the treatment.[23,38] More common side effects included: itching, red spots, congestion in the deep external auditory canal wall, and mild allergic manifestation.[38] No other studies reported any visible changes during or after treatment to the tympanic membrane. No human or animal deaths were reported in any of the included studies.

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Table 2. Study characteristics

Author (year)	Country	Subject type	Study type	Prospective or retrospective	Number of participants (ears)	Number of study groups	Number of participants (ears) by group		PBMT characteristics			Max post-PBMT follow up
							Intervention	Control (s)	Power (W)	Wavelength(s) used (nm)	Duration of PBMT	
Choi *et al.*[14] (2019)	Korea	Human	RCT	Prospective	38	2	19	19	100 mW	830	20 min/day, 5 days/ week	4 weeks
Cuda & De Caria[44] (2008)	Italy	Human	RCT	Prospective	46	2	26	20	5 mW	650	20 min/day for 90 sessions	3 months
Dejakum *et al.*[13] (2013)	Austria	Human	RCT	Prospective	48	2	22	25	450 mW	830	30 min (12 sessions over 4 weeks = 3/week)	10 weeks
Demirkol *et al.*[29] (2017)	Turkey	Human	RCT	Prospective	46	3	16	30	0.25 W	810	9 seconds/session	1 month
Eladl *et al.*[33] (2022)	Egypt	Human	RCT	Prospective	40	2	20	20	5 mW	650	20 min, 3 times weekly for 8 consecutive weeks	Not specified
Elsanadiky & Nafie[34] (2017)	Egypt	Human	Clinical cohort	Prospective	31	2	35	20	5 mW	650	25 min, 3 times within 7–10 days	7–10 days
Elsayed & Alsharif[32] (2022)	Saudi Arabia	Human	RCT	Prospective	200	2	100	100	5 mW	650	20 min/day for 60 days	60 days
Gungor *et al.*[30] (2008)	Turkey	Human	RCT	Prospective	45 (66 ears)	2	15 (21 ears)	30 (45 ears)	5 mW	650	15 min/day for 1 week	2 weeks
Mirvakili *et al.*[24] (2014)	Iran	Human	Cross-sectional RCT	Prospective	120	2	60	60	5 mW	650	20 min, 20 sessions + 3 sessions/week	5–6 months
Mirz *et al.*[23] (1999)	Denmark	Human	RCT	Prospective	50	2	25	25	50 mW	830	10 min per session/day for 5 days, then break for weekend; 15 sessions total	7 weeks
Mollasadeghi *et al.*[25] (2013)	Iran	Human	RCT	Prospective	89	2	44	45	5 mW	650	20 min/session	3 months
Montazeri *et al.*[40] (2017)	Iran	Human	Case series	Prospective	20	1	20 (35 ears)	0	100 mW	808 & 630	20 min for 12 separate sessions	12 sessions, 2 times/week
Nakashima *et al.*[36] (2002)	Japan	Human	RCT	Prospective	45 (64 ears)	2	25 (37 ears)	20 (31 ears)	60 mW	810	6 min 1 times/week for 4 sessions	4 weeks
Ngao *et al.*[35] (2014)	Malaysia	Human	RCT	Prospective	43	2	22	21	5 mW	650	20 min/day for 10 weeks	10 weeks
Okhovat *et al.*[28] (2011)	Iran	Human	Self-controlled clinical study	Prospective	61	1	61	0	5 mW	650	20 min/day for 20 days	20 days
Plath & Olivier[39] (1995)	Germany	Human	RCT	Prospective	40	2	20	20	30 W	904	8 min/day for 8 days	8 days
Rhee *et al.*[21] (2006)*	Korea	Human	RCT	Prospective	50	2	25	25	67 mW	830	20 min 3 times/week for 4 weeks	4 weeks

Salahaldin *et al.*[38] (2012)	Qatar	Human	Clinical cohort	Prospective	65	1	65 (101 ears)	0	5 mW	650	20 min/day for 3 months	3 months
Shiomi *et al.*[42] (1997)	Japan	Human	Clinical cohort	Prospective	38	3	38	0	40 mW	830	9 min once a week for 10 weeks ($n = 18$), 20 weeks ($n = 13$) or 30 weeks ($n = 7$)	1 week
Silva *et al.*[43] (2022)	Brazil	Human	RCT	Prospective	20	2	10	10	100 mW ± 20%	660–808	190 seconds, 12 sessions	6 weeks
Tauber *et al.*[27] (2003)	Germany	Human	Case series	Prospective	35	2	17 at 635 nm, 18 at 830 nm (35 ears total)	0	15–50 mW	635 or 830	Not stated. 5 times/ week for 2 weeks	2 weeks
Teggi *et al.*[37] (2009)	Italy	Human	RCT	Prospective	54	2	27	27	5 mW	650	20 min/day for 3 months	3 months
Thabit *et al.*[41] (2015)	Egypt	Human	RCT (pilot)	Prospective	30	3	20	10	200 mW	808	312 seconds	4 weeks
Toson *et al.*[31] (2016)	Egypt	Human	RCT	Prospective	60	2	30	30	–	904	20 min for 3 times/ week	1 month
Wilden & Dindinger[12] (1996)	Germany	Human	Clinical cohort	Prospective	139	1	139	0	100 mW & 20 mW helium–neon	830 & 632.8 helium–neon laser	30 min	15 days
Yıldırım *et al.*[26] (2011)	Turkey	Human	Clinical cohort	Prospective	30	1	30	0	5 mW	650	20 min	16 weeks
Park *et al.*[22] (2013)	Korea	Animal (rat)	Non-RCT	Prospective	14	2	7	7	165 mW/ cm^2	830	30 min/day for 8 days	14 days
Rhee *et al.*[21] (2006)*	Korea	Animal (guinea pig)	RCT	Prospective	20	2	10	10	67 mW	830	30 min/day for 5 days	5 days

PBMT = photobiomodulation therapy; RCT = randomised, controlled trial; min = minutes

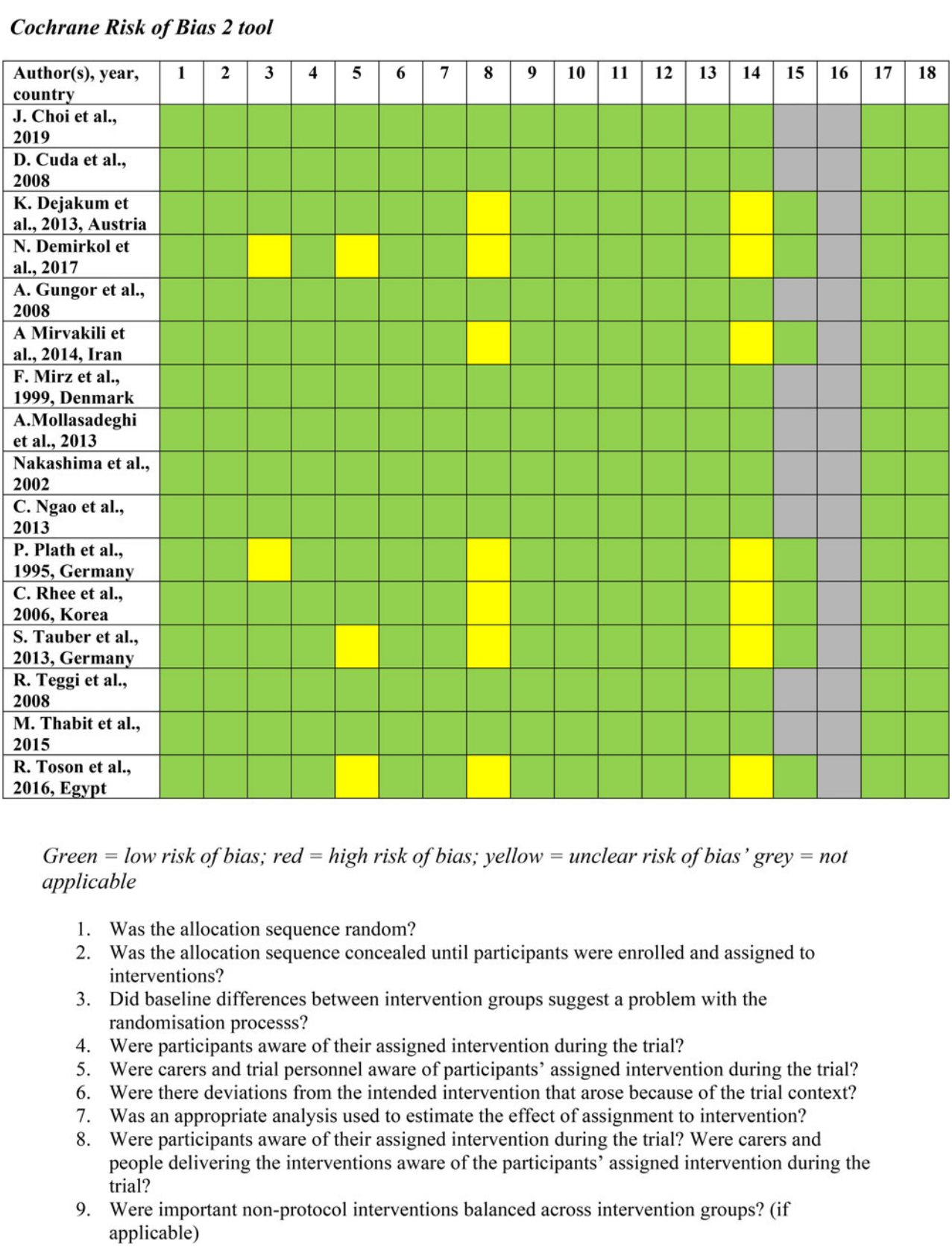

Figure 2. Cochrane Risk of Bias 2 tool.

Photobiomodulation therapy technique

Twenty-six studies outlined the photobiomodulation therapy technique and delivery method, and one study did not.[26] Five studies, including one animal study,[22] outlined the distance from the photobiomodulation therapy target site to the end of the optical fibre tip.[13,14,22,39,40] This ranged from 1 mm to 150 mm, with an average distance of 39.5 mm. All studies, except for one,[26] outlined where photobiomodulation therapy was anatomically focused onto.

Sixteen studies appropriately summarised all three of the following: wavelength used, duration of photobiomodulation therapy and follow-up period.[13,14,23–31,34,36,37,41,42] The wavelength size of 650 nm was the most used ($n = 12$).

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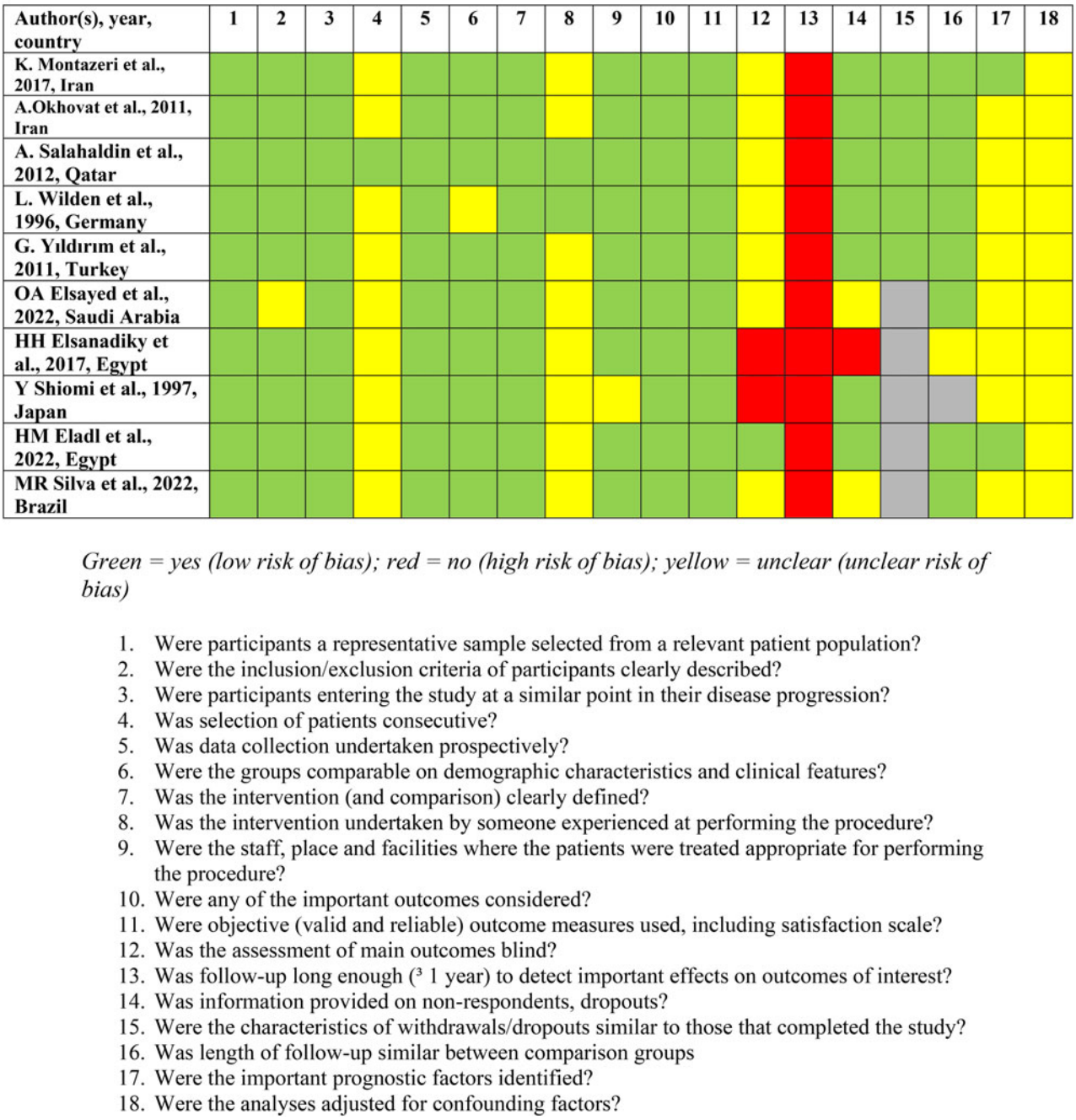
Brazzelli Risk of Bias Assessment



Green = yes (low risk of bias); red = no (high risk of bias); yellow = unclear (unclear risk of bias)

1. Were participants a representative sample selected from a relevant patient population?
2. Were the inclusion/exclusion criteria of participants clearly described?
3. Were participants entering the study at a similar point in their disease progression?
4. Was selection of patients consecutive?
5. Was data collection undertaken prospectively?
6. Were the groups comparable on demographic characteristics and clinical features?
7. Was the intervention (and comparison) clearly defined?
8. Was the intervention undertaken by someone experienced at performing the procedure?
9. Were the staff, place and facilities where the patients were treated appropriate for performing the procedure?
10. Were any of the important outcomes considered?
11. Were objective (valid and reliable) outcome measures used, including satisfaction scale?
12. Was the assessment of main outcomes blind?
13. Was follow-up long enough (³ 1 year) to detect important effects on outcomes of interest?
14. Was information provided on non-respondents, dropouts?
15. Were the characteristics of withdrawals/dropouts similar to those that completed the study?
16. Was length of follow-up similar between comparison groups
17. Were the important prognostic factors identified?
18. Were the analyses adjusted for confounding factors?

Figure 3. Brazzelli risk of bias assessment.

Photobiomodulation therapy outcomes

Photobiomodulation therapy was found to be effective in initially improving tinnitus symptoms, reducing tinnitus loudness, annoyance and duration, and improving subjective analyses in most of the included studies. One study reported a statistically significant improvement in subjective tinnitus ($p = 0.001$) following photobiomodulation therapy used in combination with an neodymium-doped yttrium aluminium garnet laser when compared to placebo ($p = 0.065$), and this combined treatment was superior to photobiomodulation therapy in isolation ($p = 0.005$).[29] Another study found that central repetitive transcranial magnetic stimulation and peripheral photobiomodulation therapy in combination was superior to either therapy in isolation, with statistical significance.[41] One study found that photobiomodulation therapy following an injection of 50 mg gingko biloba extract was superior to placebo.[39] Another study evaluated the effectiveness of a 635 nm laser or a 830 nm laser on tinnitus outcomes, and found that there was no significant difference of laser-induced effects on the degree of tinnitus between the two different wavelengths.[27]

Two studies used a combined laser technique.[12,40] One used a 630 nm diode laser and an 808 nm infrared laser to deliver photobiomodulation therapy; these lasers were applied sequentially. The results revealed a subjective short-term improvement of tinnitus.[40] One study used a combined 632.8 nm, 20 mW helium–neon, and an 830 nm, 100 mW infrared diode laser. Their results revealed a statistically significant improvement in symptom relief in the treatment group.[12]

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SYRCLE Risk of Bias Assessment

Author(s), year, country	1 Sequence generation	2 Baseline characteristics	3 Allocation concealment	4 Random housing	5 Blinding	6 Random outcome assessment	7 Blinding	8 Incomplete outcome data	9 Selective outcome reporting	10 Other sources of bias
Y. Park et al., 2013, Korea										
C. Rhee et al., 2006, Korea										

Green = yes (low risk of bias); red = no (high risk of bias); yellow = unclear (unclear risk of bias)

1. Was the allocation sequence adequately generated and applied? (*)
2. Were the groups similar at baseline or were they adjusted for confounders in the analysis?
3. Was the allocation adequately concealed? (*)
4. Were the animals randomly housed during the experiment?
5. Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?
6. Were animals selected at random for outcome assessment?
7. Was the outcome assessor blinded?
8. Were incomplete outcome data adequately addressed? (*)
9. Are reports of the study free of selective outcome reporting? (*)
10. Was the study apparently free of other problems that could result in high risk of bias? (*)

**Items in agreement with the items in the Cochrane Risk of Bias tool.*

Figure 4. Systematic Review Centre for Laboratory Animal Experimentation ('SYRCLE') risk of bias assessment.

A third study used a red wavelength of 660 nm to the tympanic membrane and an infrared wavelength of 808 nm to the mastoid tip bilaterally.[43] That study showed no significant improvement in audiological assessment findings or in subjective improvement between the intervention and placebo groups.

Ngao *et al.* assessed the effect of photobiomodulation therapy used in combination with oral betahistine 24 mg taken twice daily, which showed this was not superior to the control (sham photobiomodulation therapy device and 24 mg oral betahistine twice daily).[35]

Overall, comparisons of the photobiomodulation therapy doses indicate that higher doses have a greater positive effect on tinnitus, though methodological and statistical heterogeneity precluded meta-analysis to quantify this.

Discussion

This systematic review and narrative synthesis aimed to report on photobiomodulation therapy outcomes in the treatment of tinnitus, in both human and animal subjects. Whilst most studies reported initial improvement in tinnitus outcomes following therapy completion, few were able to demonstrate sustained improvement at follow up. Of studies that did report statistically significant sustained improvement, the longest follow-up period was one month post therapy.[29]

Photobiomodulation therapy versus placebo

Ten human studies reported photobiomodulation therapy to be superior to placebo and control groups at treating tinnitus symptoms.[14,21,24,25,29–32,39,44] Six of these reported follow-up data, including two randomised controlled trials, which noted statistically significant improvements immediately following treatment but not at the three-month follow up.[24,25]

Similarly, both animal studies reported improved outcomes, demonstrating that photobiomodulation therapy had a therapeutic effect. However, Rhee *et al.*, noted that the initial therapeutic benefit was not maintained at 24 hours' follow up. This suggests that the therapeutic benefit of photobiomodulation therapy on tinnitus may diminish over time, as has been suggested in three other studies involving two- to three- month follow-up data.[24–26]

Overall, despite differences in the results obtained from various studies, it appears there may be several factors determining whether photobiomodulation therapy success is demonstrated, including the application of proper technical parameters, correct study design methods and sufficient treatment duration.

Photobiomodulation therapy as a combination therapy

Cuda and De Caria investigated the effect of a combined counselling protocol constituting hypnotherapeutic and muscle relaxation techniques with photobiomodulation therapy.[44] They found combined therapy to be more beneficial than counselling only. These findings suggest the scope for the implementation of photobiomodulation therapy as a combination therapy in addition to patients' usual treatment. This was corroborated by Eladl *et al.*, who investigated the use of photobiomodulation therapy alongside a supervised physical therapy exercise programme compared with photobiomodulation therapy alone, demonstrating a statistically significant improvement in the former group.[33] Photobiomodulation therapy combination therapies warrant further evaluation and research to establish therapeutic benefit when compared to photobiomodulation therapy alone.

Photobiomodulation therapy positioning and characteristics

The positioning of photobiomodulation therapy for optimal delivery varies across studies. There were two main methods of irradiation reported within this systematic review. Irradiation can primarily be directed at the mastoid or across the tympanic membrane.[45] Beyer *et al.* found that irradiation of the mastoid leads to therapeutically insufficient light doses when compared to irradiation through the tympanic membrane.[45] In the animal study performed by Rhee *et al.*, no penetration was measurable through the mastoid bone.[21] Therefore, for optimum dosimetry, evaluation of the light transmission factors for chosen irradiation modalities is necessary. The externally applied light dose needs to be calculated according to the tonotopy of the cochlea as well, as different anatomical regions transduce different frequencies; this includes the position of the cochlea with respect to surface radiation portals. Further investigations are necessary in

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Table 3. Primary outcomes in human studies

Author (year)	Study data	Pre-PBMT data	Post-PBMT data	Overall benefit (subjective assessment)	Quality assessment
Choi *et al.*[14] (2019)	– Groups: 2 Group 1: PBMT ($n = 19$) Group 2: control ($n = 19$) – Investigational device: 830 nm diode laser (TINI device; Won Tech Co, Daejeon, Korea) – PBMT dose: 120 J/treatment – PBMT duration: 20 min/day, 5 days/week – Mean age of subjects: Group 1: 53.3 ± 12.9 years Group 2: 58.4 ± 11.8 years – Cause of tinnitus: Chronic unilateral tinnitus ≥3 months	– PBMT administration details: Fibre-optic catheter 10–15 mm in front of tympanic membrane, aimed at tympanic membrane toward cochlear promontory – Pre-PBMT assessment: Numerical rating scale for: *Loudness* Group 1: 5.6 ± 1.9 Group 2: 6.6 ± 1.8 *Duration* Group 1: 3.5 ± 1.0 Group 2: 3.5 ± 1.0 *Annoyance* Group 1: 5.6 ± 3.0 Group 2: 6.3 ± 2.1 – THI Group 1: 38.8 ± 25.4 Group 2: 48.4 ± 24.4	– Follow-up period – 2 weeks' follow up post intervention: – Numerical rating scale for: *Loudness* Group 1: 5.5 ± 2.0 Group 2: 5.7 ± 2.0 *Duration* Group 1: 3.0 ± 1.3 Group 2: 3.2 ± 1.0 *Annoyance* Group 1: 5.4 ± 2.8 Group 2: 5.3 ± 2.2 – THI Group 1: 34.7 ± 28.2 Group 2: 43.4 ± 20.4	Good outcomes. PBMT safe & effective in reducing duration & loudness matches of tinnitus with cochlear dysfunction. However, no significant improvement of tinnitus 2 weeks after PBMT. No placebo effect	– OCEBM grade: 1 – RoB 2 tool: low = 16, high = 0, unclear = 0
Cuda & De Caria[44] (2008)	– Groups: 2 Group 1: PBMT ($n = 26$) Group 2: control ($n = 20$) – Investigational device:650 nm laser (TinniTool EarLaser; DisMark, Maur, Switzerland)– PBMT dose: – – PBMT duration: 20 min/day for 90 sessions – Mean age of subjects: 56.4 years Males: $n = 27$ Females: $n = 19$ – Cause of tinnitus:Suffering with non-intermittent subjective tinnitus >3 months	– PBMT administration details: Probe placed at entrance of external auditory canal & laser ray directed towards tympanic membrane – Pre-PBMT assessment: Tinnitus tests (loudness, pitch match, minimum masking level) – THI Group 1: 53.6 Group 2: 43.1 – Otological evaluation & assessment	– Follow-up period – THI scores submitted at beginning & end of treatment over 3 months: – THI Group 1: 36.6 Group 2: 35.8 Group 1: 61% had tinnitus severity decrease by one class Group 2: 35% had tinnitus severity decrease by one class	Good outcomes. THI scores improved more significantly in PBMT-treated group	– OCEBM grade: 1 – RoB 2 tool: low = 16, high = 0, unclear = 0
Dejakum *et al.*[13] (2013)	– Groups: Group 1: treatment, PBMT ($n = 22$) Group 2: control, deactivated infrared laser ($n = 25$) – Investigational device: 830 nm Lasotronic (Hengersberg, Germany) – PBMT duration: 30 min (12 sessions over 4 weeks, 3 sessions/week) – PBMT power: 450 mW (9.700 J) – Mean age of subjects: 50.4 years Females: $n = 23$ Males: $n = 25$ – Cause of tinnitus:Chronic tinnitus (history >6 months)	– PBMT administration details: Laser-emitting area was 15 cm away from affected ear. Transmeatal approach – beam aimed at acoustic meatus towards tympanic membrane. In patients with bilateral tinnitus, side with higher tinnitus loudness treated. If patients could not spatially allocate their tinnitus, the right ear was treated – Pre-PBMT assessment: ENT examination Audiometric assessment Goebel's tinnitus questionnaire (tinnitus severity) VAS (tinnitus loudness) Bloods (total cholesterol, high-density lipoprotein, low-density lipoprotein & triglycerides)	– Follow-up period – 6 weeks' follow up post intervention: – Global Total Tinnitus Score (VAS score) Outcomes reported as mean. Included parameters: perceived loudness of tinnitus, annoyance associated with tinnitus, & degree of attention paid to tinnitus *Group 1:* Beginning of treatment = 35 End of treatment = 31 6 weeks post treatment = 38 *Group 2:* Beginning of treatment = 28 End of treatment = 25 6 weeks post treatment = 28 – Note: 1 patient quit after 2nd session, & not included in statistical analysis	– Uncertain outcomes. Placebo could have influenced results. No statistically significant reduction of symptoms in chronic tinnitus with PBMT – Outcomes: no statistical difference in pure tone audiometry before & after laser treatment – Low- & medium-level laser therapy does not reduce symptoms in chronic tinnitus – Conclusion: medium-level laser therapy cannot be regarded as effective treatment for chronic tinnitus	– OCEBM grade: 1 – RoB 2 tool: low = 15, high = 0, unclear = 2
Demirkol *et al.*[29] (2017)	– Groups: 3 Group 1: PBMT + Nd:YAG (1064 nm) laser Group 2: PBMT with diode laser (810 nm) Group 3: placebo	– PBMT administration details: 2 groups for PBMT administration: Nd:YAG laser (1064 nm, Fidelis Plus III; Fotona) – 810 nm diode laser (XD-2 diode laser; Fotona) 0.6 cm diameter, focal spot area: 0.282 cm^2, applied precisely & continuously into external	– Follow-up period – 1 month of follow up: – VAS (median (25–75%)), % improvement *Group 1:* 0 (0–2), 100 (60–100) ($p = 0.001$)	Good outcomes. Groups 1 & 2 were effective for treatment of subjective tinnitus when compared to placebo	– OCEBM grade: 1 – RoB 2 tool: low = 13, high = 0, unclear = 4

(*Continued*)

Table 3. (*Continued.*)

Author (year)	Study data	Pre-PBMT data	Post-PBMT data	Overall benefit (subjective assessment)	Quality assessment
	– Investigational device: 810 nm laser (XD-2 diode laser; Fotona, Ljubljana, Slovenia) – PBMT dose: – PBMT duration: Group 1: 20 seconds/session Group 2: 9 seconds/session – 5 times/week, total of 10 sessions – Mean age of subjects: 38.1 years – Cause of tinnitus: Chronic	auditory meatus for 20 seconds for Nd:YAG laser & 9 seconds for 810 nm diode laser. – 5 times per week, for a total of 10 sessions – Both used with a single-probe laser handpiece parallel to external auditory canal – Pre-PBMT assessment: VAS (median (25–75%)) Group 1: 5 (3–5.5) Group 2: 8 (4.25–9.50) Group 3: 6 (4–8)	*Group 2:* 5.5 (1.5–8), 30 (0.65.63) (p = 0.005) *Group 3:* 5 (4–7), 0 (0–22.2) (p = 0.065)		
Eladl *et al.*[33] (2022)	– Inclusion criteria: age 45–55 years, unilateral cervicogenic somatosensory tinnitus for at least 6 months – cervical pain, limited range of motion & presence of trigger points at craniocervical & occipital musculature – Groups: Group A: supervised physical therapy exercise programme + PBMT (n = 20) Group B: PBMT only (n = 20) – Investigational devices: diode laser with 650 nm wavelength (Tinnitool, DisMark, Maur, Switzerland) – PBMT power: 5 mW, 6 J energy density at tympanic membrane – PBMT duration: 20 min/session, 3 times a week for 8 consecutive weeks – Mean age of subjects: Group A: 41.25 ± 7.22 years Group B: 40.8 ± 8.08 years – Cause of tinnitus: Cervicogenic pain	– PBMT administration details: Beam transmitted into tympanic membrane with a divergent lens of 17 degrees via external auditory meatus – Pre-PBMT assessment: VAS – tinnitus annoyance & tinnitus loudness (score range of 0–10, where 10 indicates greatest impairment) –THI (range 0–100 points):Grade 1 (0–16) – slight Grade 2 (18–36) – mild Grade 3 (38–56) – moderate Grade 4 (58–76) – severe Grade 5 (78–100) – catastrophic	– Follow-up period – pre- & post-treatment assessment (at baseline & 8 weeks): – VAS *Group A* Pre-treatment: 7.44 ± 0.69 Post-treatment: 3.6 ± 0.82 p = 0.001 *Group B* Pre-treatment: 7.25 ± 0.71 Post-treatment: 5.65 ± 1.13 p = 0.001 – THI *Group A* Pre-treatment: 46.3 ± 7.61 Post-treatment: 31.05 ± 4.43 p = 0.001 *Group B* Pre-treatment: 45.9 ± 8.23 Post-treatment: 36.4 ± 5.4 p = 0.001	Good outcome: results showed a significant decrease in group A VAS & THI relative to group B (p > 0.05). Combination of physical therapy rehabilitation & PBMT should be recommended in rehabilitation protocols for treatment of chronic cervicogenic somatosensory tinnitus	– OCEBM grade: 1b – Brazzelli risk of bias checklist: low = 13, high = 1, unclear = 3
Elsanadiky & Nafie[34] (2017)	– Groups: Group 1: Control group (n = 10) Group 2: Study group (n = 21) – 7 patients with chronic unilateral tinnitus & 14 patients with chronic bilateral tinnitus – Investigational devices: TinniTool EarLaser; DisMark, Maur, Switzerland, 650 nm – PBMT power: 5 mV – PBMT duration: 25 min, 3 times within 7–10-day period – Mean age of subjects: Control group 36.5 ± 7.2 years Study group 40.24 ± 10.3 years – Cause of tinnitus: Not stated	– PBMT administration details: Emitting body equipped with a probe to be placed at entrance of external auditory canal from where laser ray was directed toward eardrum – Pre-PBMT assessment: All participants had bilateral normal hearing sensitivity (at frequency range 250–8000 Hz using AC40; Interacoustics, Middelfart, Denmark) & bilateral normal middle-ear functions (using Madsen immittancemetry; Otometrics, Taastrup, Denmark)	– Follow-up period – follow up at 2 weeks post treatment: – TEOAEs – *Study group* Pre-LLLT: 1 kHz: 9.29 ± 7 2 kHz: 8.69 ± 6.14 3 kHz: 6.54 ± 3.27 4 kHz: 3.54 ± 2.91 Overall: 17.55 ± 8.98 Post-LLLT: 1 kHz: 9.61 ± 6.98 2 kHz: 10.40 ± 6.06 3 kHz: 6.04 ± 3.87 4 kHz: 4.05 ± 3.61 Overall: 19.21 ± 7.12 – Subjective tinnitus relief:18 ears (51.4%) with subjective tinnitus reduction, 7 ears (20%) with tinnitus disappearance, & no change in 10 patients (28.6%) 2 weeks after completion of therapy	Use of LLLT was not effective objectively as recorded by TEOAEs, but showed mild improvement subjectively	– OCEBM grade: 2b – Brazzelli risk of bias checklist: low = 9, high = 3, unclear = 5

Elsayed & Alsharif[32] (2022)	– Groups: Group 1: intervention PBMT ($n = 100$) Group 2: placebo control ($n = 100$) – Investigational device: Device made in Switzerland designed by COL Company, 650 nm laser – PBMT dose: not stated – PBMT duration: 20 min/day for 60 days – PBMT power: 5 mW – Mean age of subjects: Group 1: 27.1 ± 6.4 years Group 2: 28.5 ± 7.5 years – Cause of tinnitus: Scuba diving	– PBMT administration details: Silicon tip inserted into external ear canal (depth or distance from tympanic membrane not stated) – Pre-PBMT assessment: Tinnitus Questionnaire (5-point Likert scale: 1 – not a problem, 2 – a small problem, 3 – a moderate problem, 4 – a big problem, 5 – a very big problem) completed 1 week pre-treatment, after 20 PBMT sessions, after 40 PBMT sessions & after 60 PBMT sessions	– Follow-up period – pre- & post-treatment questionnaire: – Tinnitus severity as per questionnaire – Group 1: Pre-treatment – 4.37 ± 2.02 After 20 sessions – 4.13 ± 1.92 After 40 sessions – 4.99 ± 2.11 After 60 sessions – 3.23 ± 1.64 – Group 2: Pre-treatment – 4.39 ± 2.05 After 20 sessions – 2.93 ± 1.02 After 40 sessions – 1.99 ± 0.90 After 60 sessions – 1.93 ± 0.64	Good outcome: laser therapy is easy & safe technique in treatment of tinnitus in scuba divers, & its effect increases with number of sessions of laser therapy	– OCEBM grade: 1b – Brazzelli risk of bias checklist: low = 9, high = 1, unclear = 7
Gungor *et al.*[30] (2008)	– Groups: 2 Group 1: PBMT ($n = 15$) Group 2: placebo ($n = 30$) – Investigational device: 660 nm laser (Tinnimed®) – PBMT dose: – – PBMT duration: 15 min/day over 1 week – Mean age of subjects: 55.8 years – Cause of tinnitus: Chronic unilateral or bilateral	– PBMT administration details: Irradiation of cochlea via external auditory meatus – Pre-PBMT assessment: Tinnitus loudness, duration, degree of annoyance Audiological assessment	– Follow-up period – 2 weeks' post-treatment follow up – Loudness Group 1: improvement (48.9%), no improvement (51.5%) Group 2: improvement (19.0%), no improvement (81.0%) $p < 0.05$ – DurationGroup 1: improvement (57.8%), no improvement (42.2%) Group 2: improvement (14.3%), no improvement (85.7%) $p = 0.001$– Degree of annoyance Group 1: improvement (55.6%), no improvement (44.4%) Group 2: improvement (19.0%), no improvement (81.0%) $p = 0.005$	Good outcomes. PBMT showed an effective attenuation of reported loudness, duration & degree of annoyance, with statistical significance	– OCEBM grade: 1 – RoB 2 tool: low = 16, high = 0, unclear = 0
Mirvakili *et al.*[24] (2014)	– Groups: Group 1: treatment, PBMT ($n = 60$) Group 2: control, placebo PBMT ($n = 60$) – Investigational device: 650 nm low-level laser device (Tinnimed®) – PBMT duration: 20 min/session (20 sessions, 3 sessions/week) – PBMT power: 5 mW – Mean age of subjects: 39.8 years Group 1: 41.08 ± 5.53 years Group 2: 39.43 ± 5.05 years – Group 1: Females: 30 patients (50%) Males: 30 (50%) – Group 2: Females: 29 (48.3%) Males: 31 (51.7%) – Cause of tinnitus: Tinnitus & SNHL. Chronic tinnitus. Tinnitus for >1 year due to SNHL resistant to common medical treatments	– PBMT administration details: Tip inserted inside external ear canal & laser ray radiated to internal ear & cochlea via tympanic membrane – Pre-PBMT assessment: Pure tone audiometry – Tinnitus severity Mean (SD) Group 1: 5.69 (1.35) Group 2: 6.46 (2.07) – THI grading Mean (SD) Group 1: 3.01 (1.12) Group 2: 2.73 (0.79)	– Follow-up period – 3-month follow up: – Tinnitus severity – VAS (mean (SD)) *End of intervention* Group 1: 4.28 (1.66) Group 2: 6.27 (1.99) *3 months after intervention* Group 1: 5.10 (1.85) Group 2: 6.33 (2.16) – Frequency distribution of tinnitus improvement rate per VAS (rate of at least 2 grade improvements in VAS criterion) *End of intervention* Group 1: 34 people (56.6%) Group 2: 18 people (30%) *3 months after intervention* Group 1: 16 people (26.6%) Group 2: 13 people (21%) – THI grading (mean (SD)) *End of intervention* Group 1: 1.93 (0.95) Group 2: 2.35 (0.84) *3 months after intervention* Group 1: 2.40 (1.13) Group 2: 2.43 (0.85) – Complications: No complications	– Mean difference in tinnitus severity was statistically different at end of treatment & 3 months post completion. VAS & THI mean differences were significantly significant post treatment but not at 3 months – Low-level laser radiation is effective for short-term treatment of tinnitus caused by SNHL, & its impact may be reduced over time	– OCEBM grade: 1 – RoB 2 tool: low = 15, high = 0, unclear = 2

(*Continued*)

Table 3. (*Continued.*)

Author (year)	Study data	Pre-PBMT data	Post-PBMT data	Overall benefit (subjective assessment)	Quality assessment
Mirz *et al.*[23] (1999)	– Groups: Group 1: treatment, active laser ($n = 25$) Group 2: placebo ($n = 25$) – Investigational device: 830 nm gallium-aluminium-arsenide diode laser (Uni-laser 301P, type 301.000, 3B) – PBMT duration: 10 min/session – PBMT power: 50 mW (30 J) – Mean age of subjects: 48.7 years Females: $n = 12$ Males: $n = 38$ Range = 21–72 years – Cause of tinnitus: Disabling, chronic uni- or bilateral tinnitus Cause of tinnitus not stated	– PBMT administration details: Tip of laser inserted into external acoustic meatus, beam pointed towards tympanic membrane & promontory of affected ear. One ear was treated. In subjects with bilateral tinnitus, the side of greatest matched loudness was chosen. If tinnitus loudness was symmetrical, the side with poorest hearing was selected. If hearing was symmetrical, the right side was treated – Pre-PBMT assessment: All underwent neuro-otological examination & baseline audiometric assessment Three VASs THI Tinnitus Coping Style Questionnaire Tellegen Absorption Scale State-Trait Anxiety Inventory Eysenck Personality Questionnaire Social Support Questionnaire Beck Depression Inventory	– Follow-up period – follow up at 1 month post treatment (TP5): – Tinnitus loudness (VAS) *Laser ($n = 24$):* TP1: 65.8 ± 21.4 TP2: 66.7 ± 17.5 TP3: 65.1 ± 20.5 TP4: 63.9 ± 21.3 TP5: 66.1 ± 19.4 *Placebo ($n = 24$):* TP1: 66.6 ± 24.2 TP2: 59.7 ± 23.0 TP3: 59.9 ± 26.2 TP4: 60.1 ± 30.1 TP5: 62.0 ± 27.9 – Tinnitus annoyance (VAS) *Laser ($n = 24$)* TP1: 58.4 ± 24.5 TP2: 58.4 ± 23.3 TP3: 57.9 ± 23.2 TP4: 61.0 ± 21.5 TP5: 65.9 ± 18.0 *Placebo ($n = 24$)* TP1: 63.1 ± 24.2 TP2: 54.0 ± 27.1 TP3: 58.3 ± 26.1 TP4: 55.3 ± 31.8 TP5: 63.1 ± 27.7 – Tinnitus attention (VAS) *Laser ($n = 24$):* TP1: 67.9 ± 21.8 TP2: 70.9 ± 20.2 TP3: 69.7 ± 20.4 TP4: 68.7 ± 22.0 TP5: 69.9 ± 17.8 *Placebo ($n = 24$):* TP1: 69.0 ± 23.1 TP2: 70.3 ± 23.9 TP3: 66.0 ± 27.9 TP4: 65.2 ± 28.4 TP5: 60.3 ± 30.4 – THI total *Laser ($n = 21$):* TP1: 39.8 ± 24.8 TP5: 38.8 ± 24.1 *Placebo ($n = 20$):* TP1: 45.7 ± 19.9 TP5: 38.7 ± 21.8 – THI-functional *Laser ($n = 21$):* TP1: 21.7 ± 13.7 TP5: 20.8 ± 12.5 *Placebo ($n = 20$):* TP1: 23.3 ± 9.8 TP5: 20.6 ± 10.3 *Outcomes from THI-emotional, THI-catastrophic, Beck Depression Inventory & State-Trait Anxiety Inventory are not reported here – Outcomes & complications No serious untoward adverse or side effects noted Some subjects experience warmth inside ear canal No visible changes during or after treatment to tympanic membrane	– Tinnitus was not reduced by PBMT. Those subjects reporting success in earlier studies & in this trial may have benefitted from the psychological management necessarily involved – Generally, no statistically significant effect of laser treatment on hearing between the 2 groups. However, at 4 & 8 kHz, there was a significant improvement in hearing threshold with group 1	– OCEBM grade: 1 – RoB 2 tool: low = 16, high = 0, unclear = 0

Mollasadeghi *et al.*[25] (2013)	– Groups: 2 Group 1: PBMT ($n = 44$) Group 2: Placebo ($n = 45$) – Investigational device: 650 nm laser (Tinnimed®) – PBMT dose: – – PBMT duration: 20 min/session – Mean age of subjects: 41.27 ± 5.89 years Males: $n = 89$ – Cause of tinnitus:Chronic, organic causes excluded. Mean duration: 1.85 ± 0.78 years	– PBMT administration details: irradiated to ear via mastoid bone – Pre-PBMT assessment: VAS THI Tinnitus loudness Group 1: 6.07 ± 1.12 Group 2: 6.09 ± 1.11	– Follow-up period – 3 months' follow up post treatment: – VAS *Immediately post intervention*: Group 1: no difference (54%), <50% reduction (17%), ≥50% reduction (29%) Group 2: no difference (85%), <50% reduction (7.5%), ≥50% reduction (7.5%) *3-month follow up:* Group 1: no difference (70%), <50% reduction (13%), ≥50% reduction (17%) Group 2: no difference (97%), <50% reduction (3%), ≥50% reduction (0%) – THI *Immediately post intervention*: Group 1: no difference (51%), <50% reduction (6%), ≥50% reduction (43%) Group 2: no difference (87%), <50% reduction (3%), ≥50% reduction (10%) *3-month follow up:* Group 1: no difference (66%), <50% reduction (3%), ≥50% reduction (31%) Group 2: no difference (97%), <50% reduction (0%), ≥50% reduction (3%) – Tinnitus loudness *Immediately post intervention:* Group 1: 4.51 ± 1.89 Group 2: 5.97 ± 1.03 *3-month follow up:* Group 1: 5.09 ± 1.90 Group 2: 6.02 ± 1.15	Good outcomes. PBMT effective in alleviating tinnitus in noise-induced hearing loss patients; however, effect faded after 3 months' follow up. Despite improvement, PBMT non-response rate still considerable	– OCEBM grade: 1– RoB 2 tool: low = 16, high = 0, unclear = 0
Montazeri *et al.*[40] (2017)	– Groups: 1 Group 1: PBMT intervention ($n = 20$) – Investigational device: 630 nm diode laser included PR-100 Red laser by COL Company. 808 nm PR-100 infrared laser designed by COL Company – PBMT dose: 120 J/ear/session – PBMT duration: 20 min/session – PBMT power: 100 mW (density = 0.1 W/cm^2) – Mean age of subjects: 45.7 ± 9.35 years Females: $n = 5$ Males: $n = 15$ Range = 33–84 years – Cause of tinnitus: Intractable permanent chronic unilateral or bilateral moderate to severe tinnitus, present for >6 months. Exact cause not stated. – Tinnitus characteristics: Left ear ($n = 2$) Right ear ($n = 3$) Bilaterally ($n = 15$)	– PBMT administration details: 2 wavelengths applied sequentially, first infrared (808 nm), followed by red laser (630 nm). Infrared laser positioned on 3 points of mastoid bone: (1) on the mastoid bone at level of auricle behind ear; (2) 3 cm above the first point; (3) 3 cm below the first point. Laser was applied to each point for 5 min (30 J/point). Red laser was then irradiated directly to ear canal for 5 min (30 J) – Pre-PBMT assessment: VAS LMT Pitch matching of tinnitus Persian Tinnitus Questionnaire Persian THI DPOAE Electrocochleography	– Follow-up period not stated – Answers are reported as mean ± SD – VAS for loudness: Pre-PBMT: 5.7 ± 1.5 Post-PBMT: 3.2 ± 2.3 – LMT: Pre-PBMT: 5.5 ± 1.6 Post-PBMT: 4 ± 1.8 – Persian Tinnitus Questionnaire: Pre-PBMT: 65.7 ± 13.7 Post-PBMT: 50.2 ± 17.7 – Persian THI: Pre-PBMT: 68.6 ± 15.2 Post-PBMT: 54.6 ± 13.7 – Compound action potential amplitude: Pre-PBMT: 0.25 ± 0.1 Post-PBMT: 0.51 ± 0.1 – Compound action potential threshold: Pre-PBMT: 46.9 ± 3.3 Post-PBMT: 46.8 ± 2.8 – DPOAEs *1001 Hz* Pre-PBMT: 1.85 ± 7.2 Post-PBMT: 1.54 ± 5.32 *2002 Hz* Pre-PBMT: 6.29 ± 5.53 Post-PBMT: 3.40 ± 8.85 *4004 Hz* Pre-PBMT: −2.37 ± 5.08 Post-PBMT: −5.35 ± 4.38	– PBMT may be a subjectively effective treatment for short-term improvement of tinnitus – Compound action potential threshold & DPOAEs were not statistically significant – VAS, LMT, Persian Tinnitus Questionnaire, Persian THI & compound action potential amplitude were statistically significant – Statistical analyses revealed significant differences for subjective evaluating parameters & compound action potential amplitude – Note: unusual as based upon pre- & post-treatment VAS scores for loudness & LMT. They were split into 2 groups: positive result & negative result	– OCEBM grade: 3 (case series) – Brazzelli risk of bias checklist: low = 13, high = 1, unclear = 4

(*Continued*)

Table 3. (*Continued.*)

Author (year)	Study data	Pre-PBMT data	Post-PBMT data	Overall benefit (subjective assessment)	Quality assessment
Nakashima *et al.*[36] (2002)	– Groups: 2 Group 1: PBMT ($n = 25$) Group 2: placebo ($n = 20$) – Investigational device: 810 nm laser (Softlasery JQ 310; Minato Medical Science Co, Osaka, Japan) – PBMT dose: – PBMT duration: 6 min, 1 time/week for 4 sessions – Mean age of subjects: Group 1: 52.4 Group 2: 55.2 – Cause of tinnitus: –	– PBMT administration details: Transmeatal delivery of PBMT – Pre-PBMT assessment: Assessment of: loudness, duration, quality, annoyance of tinnitus	– Follow-up period – follow up at 1-week post treatment: PBMT group improvement: 9/31 (29.03%) Placebo group improvement: 9/33 (27.27%) – Loudness & annoyance ratings did not differ significantly between the 2 treatment groups	– PBMT with 60 mW was not effective for treatment of tinnitus. No significant difference was observed between active & placebo laser groups	– OCEBM grade: 1 – RoB 2 tool: low = 16, high = 0, unclear = 0
Ngao *et al.*[35] (2014)	– Groups: 2 Group 1: PBMT + oral betahistine 24 mg BD ($n = 22$) Group 2: control (sham PBMT device + oral betahistine 24 mg BD) ($n = 21$) – Investigational device: 650 nm Tinnitool MedicLaser; DisMark, Maur, Switzerland) – PBMT dose: – PBMT duration: 20 min/day, 10 weeks & oral betahistine 24 mg BD – Mean age of subjects: – – Cause of tinnitus: –	– PBMT administration details: Subject had wearable head band directing PBMT through external ear canal, & into inner ear – Pre-PBMT assessment: Pure tone audiogram THI (mean) Group 1 (40) Group 2 (42) VAS	– Follow-up period – pre- & post-intervention questionnaire (10 weeks' therapy): – THI *Group 1:* Significant decrease when compared to initial value ($p = 0.038$) Improvement ($n = 12$) No improvement ($n = 7$) Worse ($n = 3$) *Group 2:* Improvement ($n = 17$) No improvement ($n = 2$) Worse ($n = 2$) – VAS Subjects in groups 1 & 2 reported either improvement or no change in all symptoms assessed. Decrease in severity was not statistically significant, except patients in group 2	PBMT was not significantly superior to placebo effect in improving tinnitus	– OCEBM grade: 1 – RoB 2 tool: low = 16, high = 0, unclear = 0
Okhovat *et al.*[28] (2011)	– Groups: 1 Group 1: PBMT ($n = 61$) – Investigational device: 650 nm laser (Tinnimed®) – PBMT duration: 20 min/day for 20 days – Mean age of subjects: 40.5 ± 15.3 years Males: $n = 38$ Females: $n = 23$ – Cause of tinnitus:Chronic: monoliteral or bilateral tinnitus >6 months. Ruled out treatable causes of tinnitus	– PBMT administration details: Directed through tympanic membrane into cochlea – Pre-PBMT assessment: Tinnitus VAS: 82.3 ± 18.3 Audiometric assessment Microscopic examination of external auditory meatus & tympanic membrane	– Follow-up period – 2 weeks post treatment: – Tinnitus VAS mean reduction in: Males: 31.3% Females: 43.6% Tinnitus intensity: 35.9% – Tinnitus symptoms completely disappeared in 11 subjects	Good outcomes. Results were statistically significant. Overall, PBMT is effective for tinnitus, but variables such as age & job can affect outcomes. No adverse effects observed	– OCEBM grade: 2 – Brazzelli risk of bias checklist: low = 12, high = 1, unclear = 5
Plath & Olivier[39] (1995)	– Groups: 2 Group 1: intervention, PBMT after injection of 50 mg gingko Biloba extract ($n = 20$) Group 2: control, sham laser irradiation & injection of gingko Biloba ($n = 20$) – Investigational device: Combined helium–neon (continuous wave, 632.5 nm, 12 mW output) & gallium arsenide laser (5 impulse regulated gallium arsenide infrared laser diodes, 904 nm, rated impulse power 30 W, frequency 100–2800 Hz) – PBMT dose: 904 nm – PBMT duration: 8 min/day for 8 days – Mean age of subjects: not stated Females: $n = 15$ Males: $n = 25$	– PBMT administration details: Distance between laser head & skin = 2 cm Direction of laser beam lead from 4 cm above point of corresponding mastoid to lateral rim of opposite orbit – Pre-PBMT assessment: Tone audiometry Tympanometry Brainstem evoked response audiometry Analysis of tinnitus in regard to its main frequency, loudness & masking intensity of narrow band noise	– Follow-up period – pre- & post-treatment assessment: – Tinnitus Group 1: reduction of >10 dB in 50%, reduction >20 dB ($n = 6$), complete relief ($n = 2$) Group 2: reduction >10 dB in 5%, reduction >10 dB ($n = 1$), complete relief ($n = 0$) – Self-assessment in comparison with audiometry Group 1: reduction in tinnitus ($n = 12$) Group 2: reduction in tinnitus ($n = 5$)	– Good outcomes. PBMT appears to improve tinnitus symptoms	– OCEBM grade: 1 – RoB 2 tool: low = 14, high = 0, unclear = 3

	– Cause of tinnitus: Chronic tinnitus, lasting for 6 months to 5 years, with SNHL. All patients had little or no response to range of treatment				
Rhee *et al.*[21] (2006)*	– Groups: Group 1: control ($n = 25$) Group 2: laser ($n = 25$) – Investigational device: 830 nm diode laser EIT 21 (Shinsung, Seoul, Korea) – PBMT dose: 80.4 J/cm^2 – PBMT duration: 20 min, 3 times/week for 4 weeks – PBMT power: 67 mW – Mean age of subjects: 50.8 years – Cause of tinnitus: Not statedUnilateral = 70% of subjects	– PBMT administration details: All patients were administered gingko biloba extract orally. Group 2 received transmeatal PBMT therapy. Laser aimed into external auditory canal of affected ear towards tympanic membrane & promontory – Pre-PBMT assessment: – VAS *Loudness* Group 1: 5.8 ± 2.6 Group 2: 5.4 ± 1.8 *Duration* Group 1: 9.2 ± 3.1 Group 2: 9.6 ± 2.9 – THI Group 1: 54.6 ± 29.9 Group 2: 61.6 ± 24.8	Follow-up period – pre- & post-treatment follow up only:– VAS *Loudness*Group 1: 5.5 ± 2.6 Group 2: 2.7 ± 1.1 *Duration* Group 1: 8.8 ± 3.0 Group 2: 8.0 ± 2.2– THI Group 1: 47.6 ± 27.4 Group 2: 48.9 ± 23.2 – Overall improved feeling of tinnitus: Group 1: 4/25 subjects Group 2: 14/25 subjects (56%) Completed before & 1 week after final PBMT therapy	– Good outcomes – Significant decrease in tinnitus loudness (VAS score) & THI in group 2. Overall improved feeling of tinnitus was significant in group 2 participants. Duration of tinnitus (VAS) change not statistically significant in group 2 – PBMT appears to be beneficial in reducing loudness & degree of annoyance from tinnitus	– OCEBM grade: 1 – RoB 2 tool: low = 15, high = 0, unclear = 2
Salahaldin *et al.*[38] (2012)	– Groups: Group 1: PBMT intervention ($n = 65$) – Investigational device: 650 nm Tinnitool diode laser (Dismark, Maur, Switzerland) – PBMT dose: 6 J at tympanic membrane – PBMT duration: 20 min/day for 3 months – PBMT power: 5 mW – Mean age of subjects: Range = 15–76 years 101 ears – Cause of tinnitus: Patients had chronic unilateral or bilateral tinnitus with a minimum duration of 1 year & were not responding to conventional therapy. Cause was known: Ménière's disease ($n = 19$), sudden SNHL ($n = 15$), associated with sensorineural hearing impairment ($n = 32$), tinnitus due to sensorineural hearing impairment with causes other than above ($n = 6$)	– PBMT administration details: Applied transmeatally. Laser beam projected into tympanic membrane through a 17-degree divergent lens creating a spot size of 1 cm^2 – Pre-PBMT assessment:Not stated	– Follow-up period – interval assessment during 3-month treatment period: – Audiometric hearing improvement of: 8 dB for low & high frequencies in 44 & 39 audiograms 5 dB in 41 audiograms No response in 21, 23 & 21 audiograms 3 dB hearing deterioration in 20, 18 & 27 audiograms – Subjective improvement: No improvement ($n = 18$, 43.1%) Mild improvement ($n = 22$, 33.8%) Moderate improvement ($n = 11$, 16.9%) Full improvement ($n = 4$, 6.15%) – Improvement in dizzy spells: No improvement ($n = 15$, 23.07%) Mild improvement ($n = 18$, 27.69%) Moderate improvement ($n = 2$, 3.07%) Full improvement ($n = 11$, 16.92%) Deteriorated ($n = 2$, 3.07%) Had no dizziness to begin with ($n = 17$, 26.16%) – Side effects: Itching, red spots, congestion in deep external auditory canal wall, mild allergic manifestation, increased tinnitus & hyperacusis	– Good outcomes – PBMT appears to be useful in treatment of chronic tinnitus – Study showed significant improvement of hearing threshold level in patients with tinnitus, namely in cases of Ménière's disease & sudden SNHL & other patients with tinnitus due to SNHL (49.2%). Reduction in loudness & annoyance in 37 patients, with complete disappearance in 4. Effective in reducing dizziness	– OCEBM grade: 2 – Brazzelli risk of bias checklist: low = 14, high = 1, unclear = 3
Shiomi *et al.*[42] (1997)	– Groups: 1 Group 1: 38 patients with tinnitus associated with SNHL resistant to medical therapy for >6 months – Investigational devices: Mochida laser apparatus, 830 nm – PBMT power: 40 mW – PBMT duration: 9 min once a week. 18 patients had 10 sessions, 13 patients had 20 sessions & 7 patients had 30 sessions – Mean age of subjects: 56 ± 2.0 years – Cause of tinnitus: Not stated	– PBMT administration details: Cochlea irradiated via external auditory meatus (no further details given) – Pre-PBMT assessment: Participants completed a questionnaire using a 5-point Likert scale assessing loudness, duration & 'degree of annoyance' before & after therapy	– Follow-up period – follow up at 1-week post treatment: – Tinnitus questionnaire *Loudness:* Less (%): 58 Same (%): 39 More (%): 3 *Duration:* Less (%): 26 Same (%): 74 More (%): 0 *Degree of annoyance:*	Good outcome: improvement in 60% patients without major complications	– OCEBM grade: 2b – Brazzelli risk of bias checklist: low = 9, high = 2, unclear = 5

(*Continued*)

Table 3. (*Continued.*)

Author (year)	Study data	Pre-PBMT data	Post-PBMT data	Overall benefit (subjective assessment)	Quality assessment
			Less (%): 55 Same (%): 42 More (%): 3		
Silva *et al.*[43] (2022)	– Inclusion criteria: completed informed consent form; normal bilateral audiometry with ISO mean (0.5, 1, 2 & 4 kHz) up to 25 dB); complaint of continuous tinnitus for at least 6 months; age 18 years or older – Groups: Group 1: 10 participants receiving active laser protocol (intervention) Group 2: 10 participants receiving light protocol with negligible power (placebo) – Investigational devices: direct current Therapy EC Laser – PBMT power: 100 mW ± 20% (660 nm & 808 nm) – PBMT duration: 12 sessions each lasting 190 seconds total – Mean age of subjects: Group 1: median age, 54 years Group 2: median age, 58 years	– PBMT administration details: application of continuous wave laser diode, at red wavelength (660 nm), was carried out only once, directly on right & left lingual veins (energy = 2 J & time = 20 seconds), with purpose of systemic action. Subsequently, left tympanic membrane (E = 4 J, t = 40 seconds) was irradiated at red wavelength, followed by left & right mastoid (E = 9 J, t = 90 seconds) at infrared wavelength (808 nm), & ending with irradiation of right tympanic membrane (E = 4 J, t = 40 seconds) at red wavelength (660 nm) – Pre-PBMT assessment: all patients underwent a battery of audiological tests, which included visual inspection of external auditory canal to discard any impediment in outer ear &/or in middle ear, pure tone audiometry, high-frequency audiometry, immittanciometry, & acuphenometry. In addition, THI	– Follow-up period – pre- & post-treatment follow up: – THI *Group 1:* Initial – 18.00 ± 11.33 Final – 11.90 ± 10.08 *Group 2:* Initial – 22.30 ± 9.73 Final – 16.90 ± 7.48 – Acuphenometry *Group 1:* Right acuphenometry Initial – 23.00 ± 20.44 Final – 17.00 ± 14.57 Left acuphenometry Initial – 17.50 ± 17.20 Final – 12.50 ± 10.07 *Group 2:* Right acuphenometry Initial – 17.00 ± 18.59 Final – 12.50 ± 10.07 Left acuphenometry Initial – 15.50 ± 16.74 Final – 13.50 ± 14.73	– Good outcome – There was also a significantly higher reduction in perception of level of satisfaction with tinnitus in initial sessions compared to final sessions in group that received PBMT	– OCEBM grade: 1b – Brazzelli risk of bias checklist: low = 10, high = 1, unclear = 5
Tauber *et al.*[27] (2003)	– Groups: 2 Group 1: 635 nm laser (*n* = 17) Group 2: 830 nm laser (*n* = 18) – Investigational device: 635 or 830 nm laser – PBMT dose: not stated. – PBMT duration: Not stated how long per session. 5 times a week for 2 weeks – Mean age of subjects: 46 ± 12 years Male:female ratio = 1.4:1 – Cause of tinnitus:Not stated	– PBMT administration details: Positioned to external auditory meatus using a headset applicator & laser aimed at tympanic membrane – Pre-PBMT assessment:Tinnitus VAS	– Follow-up period – 6-month follow-up period: – Tinnitus VAS *After PBMT:* Unchanged (34%) Decreased (51%) Absent (6%) Increased (9%) – *1 week follow up:* Unchanged (37%) Decreased (49%) Absent (6%) Increased (9%) – *6-month follow up:* Unchanged (57%) Decreased (37%) Absent (6%) – Audiometric assessment *6-month follow up:* Unchanged (57) Significant improvement (26%) Significant modulation (11%) Absent (6%) – All observed effects were similar in both treatment groups & were independent of laser wavelength	– Good outcomes – Changes of tinnitus loudness & tinnitus matching have been described. After a 6-month follow-up period, tinnitus loudness was attenuated in 13 of 35 irradiated patients, whilst 2 of 35 patients reported their tinnitus as totally absent	– OCEBM grade: 1 – RoB 2 tool: low = 14, high = 0, unclear = 3
Teggi *et al.*[37] (2009)	– Groups: 2 Group 1: PBMT (*n* = 27) Group 2: control (*n* = 27) – Investigational device: 650 nm diode TinniTool soft laser (DisMark, Maur, Switzerland)	– PBMT administration details: Projected onto tympanic membrane – Pre-PBMT assessment: – THI Group 1: 42.5 ± 24.2 Group 2: 51.5 ± 36.6	– Follow-up period – 3 months' follow up: – THI Group 1: 33.7 ± 26.1 Group 2: 42.8 ± 24.3	– Study demonstrated PBMT did not show significant efficacy for its use in treatment for tinnitus – No significant difference between groups 1 & 2	– OCEBM grade: 1 – RoB 2 tool: low = 16, high = 0, unclear = 0

	– PBMT dose: 6 J/session – PBMT duration: 20 min/day for 3 months – Mean age of subjects: Group 1: 51.6 ± 11.3 years Group 2: 53.1 ± 12.9 years – Cause of tinnitus: Acute & chronic	– Pure tone audiometry – Psychoacoustic assessment: *Loudness (dB)* Group 1: 6.07 ± 5.28 Group 2: 6.16 ± 4.5 *Minimum masking level* Group 1: 8.9 ± 5.7 Group 2: 8.8 ± 5.4 – VAS Group 1: 63.7 ± 21.8 Group 2: 61.9 ± 20.3	– Psychoacoustic assessment: *Loudness (dB)* Group 1: 3.77 ± 2.0 Group 2: 6.68 ± 5.6 *Minimum masking level* Group 1: 6.2 ± 3.4 Group 2: 7.4 ± 4.3 – VAS Group 1: 62.9 ± 23.8 Group 2: 58.8 ± 22.6		
Thabit *et al.*[41] (2015)	– Groups: 3 Group 1: repetitive TMS + PBMT ($n = 10$) Group 2: repetitive TMS ($n = 10$) Group 3: PBMT ($n = 10$) – Investigational device: 808 nm Polaris 2 device (Astar Physiotechnology, Bielsko-Biała, Poland) – PBMT dose: 40 J/cm^2 – PBMT duration: 312 seconds/session – Mean age of subjects: Group 1: 38.7 ± 13.6 years Group 2: 40.7 ± 12 years Group 3: 36.4 ± 14.7 years – Cause of tinnitus: Subjective unilateral or bilateral, non-pulsatile, chronic tinnitus (>6 months) with normal neurological examination findings	– PBMT administration details: 5 locations: external auditory meatus & 4 acupuncture points that are related to hearing disorders: (1) highest point in depression between angle of mandible & mastoid bone (SJ 17 Chinese map of acupuncture points); (2) temporomandibular joint when mouth is slightly opened (SI 19); (3) depression in front of supratargic notch (SJ 21); & (4) above auricle (SJ 20) – Pre-PBMT assessment: – THI Group 1: 66.6 ± 7.1 Group 2: 72.2 ± 5.1 Group 3: 73.1 ± 4.3 – VAS Group 1: 66.1 ± 7.9 Group 2: 69.4 ± 5 Group 3: 66.9 ± 4.9	– Follow-up period – 4-week follow up: – THI 4 weeks post PBMT: Group 1: 41.4 ± 7.5 Group 2: 61.3 ± 5.9 Group 3: 66.7 ± 4.6 – VAS 4 weeks post PBMT: Group 1: 41.4 ± 6.2 Group 2: 62.1 ± 5.4 Group 3: 61.6 ± 4.7	– Good outcomes – Study suggests combined central repetitive TMS & peripheral PBMT is superior to either therapy in isolation	– OCEBM grade: c – RoB 2 tool: low = 16, high = 0, unclear = 0
Toson *et al.*[31] (2016)	– Groups: 2 Group 1: intervention, PBMT ($n = 30$) Group 2: control, placebo laser ($n = 30$) – Investigational device: 904 nm infrared laser – PBMT dose: not stated – PBMT duration: 20 min, 3 times/week – PBMT power: not stated – Mean age of subjects: Range = 30–50 years Group 1: 38.43 ± 6.42 years Group 2: 40.1 ± 6 years Females: $n = 30$ Males: $n = 30$ – Cause of tinnitus: Chronic subjective monoliteral or bilateral tinnitus with or without SNHL	– PBMT administration details: Laser device was fixed on processus mastoideus. Just the influenced ear was treated. If patients were unable to spatially determine their tinnitus, the right ear was the default treatment side – Pre-PBMT assessment: VAS Group 1: 7.2 ± 1.73 Group 2: 7.4 ± 1.97 – Tinnitus Severity Index Median (range) Group 1: 40 (27) Group 2: 43.5 (28)	– Follow-up period – follow up at 1-month post treatment: – VAS: Group 1: 3.2 ± 2.68 (55.55% change) Group 2: 6.53 ± 2.28 (11.75% change) – Tinnitus Severity Index: Median (range) Group 1: 25 (28) Group 2: 41 (27)	– Good outcomes – There was a significant decrease in VAS & Tinnitus Severity Index outcomes in group 1 compared to group 2. PBMT has a significant improvement in chronic subjective tinnitus	– OCEBM grade: 1 – RoB 2 tool: low = 14, high = 0, unclear = 3
Wilden & Dindinger[12] (1996)	– Groups: 1 Group 1: intervention, PBMT ($n = 139$) – Investigational device: Combined 632.8 nm, 20 mW helium–neon & 830 nm, 100 mW infrared diode lasers – PBMT dose: 96 J over mastoid & 19 J over external meatus – PBMT duration: 30 min/session (15 treatments) – PBMT power: 100 mW – Mean age of subjects: not stated – Cause of tinnitus: Not stated. All patients had received usual conventional treatment	– PBMT administration details: 20 min to mastoid over an area of 1 cm, & 10 min at external meatus – In addition to PBMT, they were also given plant-based drug (gingkoflavonglycoside) – Pre-PBMT assessment: General well-being Tinnitus therapy level Vertigo therapy level Audiometry	– Follow-up period – pre- & post-treatment questionnaires: – General well-being: Significant improvement: 77.4%(2.1% excellent; 31.2% much improved; 44.1% noticeable improvement) Little or no improvement: 20.4% Worse following treatment: 2.2%– Level of tinnitus: Significant improvement: 67.8% (2.2% excellent; 14% much improved; 51.6% noticeable improvement) Little or no improvement: 30.1% Exacerbation of tinnitus: 2.1%	– Good outcomes – Appears to be an effective treatment for tinnitus	– OCEBM grade: 2 – Brazzelli risk of bias checklist: low = 12, high = 1, unclear = 5

(*Continued*)

Table 3. (*Continued.*)

Author (year)	Study data	Pre-PBMT data	Post-PBMT data	Overall benefit (subjective assessment)	Quality assessment
			– Level of vertigo: Significant improvement: 82.5% (27.5% excellent; 22.5% much improved; 32.5% noticeable improvement) Little or no improvement: 17.5% Exacerbation of vertigo: 0% – Audiometry: Statistically significant improvement in hearing of 20 dB in all frequencies documented in 83% of patients		
Yıldırım *et al.*[26] (2011)	– Groups: 1 Group 1: intervention, PBMT ($n = 30$) (Patients were divided into 4 groups based on age; however, all received same treatment) – Investigational device: 650 nm laser – PBMT dose: – PBMT duration: 20 min/day for 8 weeks, excluding weekends Total sessions ($n = 40$) – Mean age of subjects: 42.93 years Range: 20–74 years Female: 15 Male: 15 – Cause of tinnitus: Chronic tinnitus.Unilateral (left) ($n = 7$) Unilateral (right) ($n = 11$) Bilateral = ($n = 12$)	– PBMT administration details: Not stated – Pre-PBMT assessment: – Pure tone audiometric evaluation at 0.25–20 kHz – Tinnitus VAS	– Follow-up period – 2-month post-treatment follow up: – Pure tone audiometry Results between males & females not significant Significant difference after therapy ($p < 0.001$) Significant difference between males & females after laser therapy – Tinnitus VAS 50.8% positive change in tinnitus	– Good outcomes – PBMT appears effective right after therapy. However, audiometric values returned to pre-treatment levels after 2 months, & tinnitus scores remained lower compared to pre-treatment scores	– OCEBM grade: 2b? – Brazzelli risk of bias checklist: low = 12, high = 1, unclear = 5

PBMT = photobiomodulation therapy; min = minutes; OCEBM = Oxford Centre for Evidence Based Medicine; RoB 2 = Cochrane Risk of Bias 2; THI = Tinnitus Handicap Inventory; VAS = visual analogue scale; Nd:YAG = neodymium-doped yttrium aluminium garnet; TEOAE = transient evoked otoacoustic emissions; LLLT = low-level laser therapy; SNHL = sensorineural hearing loss; SD = standard deviation; LMT = loudness matching of tinnitus; DPOAE = distortion product otoacoustic emissions; BD = twice daily; TMS = transcranial magnetic stimulation

Table 4. Primary outcomes in animal studies

Author (year)	Study data	Pre-PBMT data	Post-PBMT data	Overall benefit (subjective assessment)	Quality assessment
Park *et al.*[22] (2013)	– Groups: Group 1: control ($n = 7$) Group 2: intervention, PBMT ($n = 7$) – Investigational device: 830 nm diode laser (Hi-Tech Optoelectronics, Beijing, China) – PBMT duration: 30 min/day for 8 days – PBMT power: 165 mW/cm^2 – Mean age of subjects: 8 weeks – Cause of tinnitus: Salicylate-induced tinnitus	– PBMT administration details: Rats given 400 mg/kg/day of sodium salicylate for 8 consecutive days. Group 2 was irradiated to both ears with 850 nm diode laser. Delivered through external acoustic canal. Tip to eardrum was 1 mm – Pre-PBMT assessment: Auditory brainstem response – GPIAS: Group 1: 60.9% Group 2: 62.6%	Follow-up period – 24 hours post final injection: GPIAS: *Group 1:* Day 1: 6.1%, day 2: 17.3%, day 3: 28.1%, day 4: 22.2%, day 5: 18.9%, day 6: 16.6%, day 7: 17.9%, day 8: 17.2% *Group 2:* Day 1: 6.7%, day 2: 40.7%, day 3: 36.7%, day 4: 44:0%, day 5: 49.2%, day 6: 44.8%, day 7: 45.6%, day 8: 40.3%	Good outcomes Therapeutic effect of LLLT is demonstrated in animal tinnitus model by means of GPIAS. Further experimental studies are needed to find possible mechanisms & better methods to improve LLLT efficacy During entire duration of experiment, group 2 showed significantly higher mean GPIAS values than group 1	– OCEBM grade: 1 – SYRCLE's risk of bias tool: Low = 5; high = 0; unclear = 5
Rhee *et al.*[21] (2006)*	– Groups: Group 1: control ($n = 10$) Group 2: intervention, PBMT ($n = 10$) – Investigational device: 830 nm diode laser (EIT 21; Shinsung, Seoul, Korea) – PBMT dose: 120.6 J/cm^2 – PBMT duration: 30 min – PBMT power: 67 mW/cm^2 – Mean age of subjects: not stated – Cause of tinnitus: Gentamicin-induced vestibular ototoxicity	– PBMT administration details: Both groups had gentamicin 2.4 mg injected into left middle-ear cavity through tympanic membrane once a day for 2 days PBMT irradiated to external ear canal opening. Transmeatal delivery – Pre-PBMT assessment: Not stated	– Follow-up period – follow-up period not stated: – Values of gain in slow harmonic acceleration rotation test: *Group 1:* Left = 0.55 ($p < 0.05$) Right = 0.8 *Group 2:* Left = 0.71 Right = 0.76 – Values of modulation in off-vertical axis rotation test: *Group 1:* Left = 0.57 Right = 0.65 *Group 2:* Left = 0.75 Right = 0.64	– Good outcomes – Demonstrated protective effects of PBMT against gentamicin-induced toxicity	– OCEBM grade: 1 – SYRCLE's risk of bias tool: Low = 6; high = 0; unclear = 4

PBMT = photobiomodulation therapy; min = minutes; GPIAS = gap pre-pulse inhibition of acoustic startle; LLLT = low-level laser therapy; OCEBM = Oxford Centre for Evidence Based Medicine; SYRCLE = Systematic Review Centre for Laboratory Animal Experimentation

order to determine the optimum light doses for photobiomodulation therapy.

The wavelength of the laser is comparable with the chemical composition of a drug, and the power is comparable to the dosage of a drug. A drug will not be effective if either the chemical composition or dosage is incorrect. Similarly, as in a drug overdose, an excess amount of laser irradiation may lead to destruction rather than promotion.[46] Consequently, determining photobiomodulation therapy parameters is important, although there will likely be a large amount of overhead between therapeutic and toxic doses. These parameters must be balanced with the challenges of delivering photobiomodulation therapy safely. It is widely known that there is a typical responsive wavelength for cytochrome c oxidase (approximately 670 nm);[9] nonetheless, this wavelength is within the visible light range and has a lower tissue penetrance than the near-infrared range.[9] Cytochrome c oxidase mediates photobiomodulation in the far red and near-infrared range. Therefore, it becomes difficult to deliver a laser of this wavelength to the otic capsule if it must penetrate the tympanic membrane, bone and other tissues.[47] Wavelengths must be carefully selected according to how the photobiomodulation therapy will be delivered, what it is targeting, and which structures the light must pass through to reach the cochlea.

Additionally, it is important to ascertain whether shorter, concentrated bursts of delivery of photobiomodulation therapy induces a greater significant effect on tinnitus symptoms when compared to a prolonged delivery.

Tinnitus assessment tools

A total of 11 different assessment tools were noted to be used across all studies, resulting in inconsistency in outcome measures. Choosing a suitable assessment tool plays an important role in evaluating therapeutic effects. Tinnitus is a subjective perception; therefore, a patient's estimation of it is highly individual. Subjective evaluation tools are valuable for monitoring therapeutic effects. However, one study reported that tinnitus subjects encountered difficulties in rating their subjective perceptions on VAS, which could introduce error.[40] Consequently, it is important to consider the use of objective assessment measures (e.g. electroencephalograph markers) before and after photobiomodulation therapy in tinnitus subjects. These, however, are not yet considered robust.

Future of photobiomodulation therapy

Overall, the heterogeneity of study design, including tinnitus outcome measures, photobiomodulation therapy duration, power and wavelength, precludes definitive conclusions on photobiomodulation therapy efficacy in the treatment of tinnitus. Most studies to date have been conducted on human models. The majority assessed outcomes over a short length of time, with the longest follow-up period being six months. This relatively short duration precludes comment on the long-term effects that photobiomodulation therapy may have on resolving tinnitus symptoms, or whether further courses are needed to suppress tinnitus returning and maintain individuals' therapeutic response. Most human studies concluded that the short-term effects of photobiomodulation therapy had a positive effect on tinnitus outcomes. The follow-up period across the studies included is low and therefore long-term outcomes of photobiomodulation therapy could not be evaluated. Enabling a follow-up period of at least a year will allow researchers to assess the longer-term effects and complications of photobiomodulation therapy. Further robust trials with consistency in terms of photobiomodulation therapy parameters, tinnitus assessment tools and follow-up period are essential for the evaluation of photobiomodulation therapy in the management of tinnitus.

Conclusion

Whilst tinnitus outcomes following photobiomodulation therapy appear to be superior to non-photobiomodulation therapy in most studies, inconsistencies in study design and short follow-up duration preclude definitive consensus. With tinnitus affecting 1 in 10 adults, and with limited treatments proven to show benefit, the demand for treatment and solutions for tinnitus symptoms is paramount. It is imperative that solutions are sought that incur minimal risks and damage to patients. The minimal risk profile of photobiomodulation therapy to date highlights its promising use in the field of otolaryngology. It is essential that further research considers the optimal design, duration, position and follow up of photobiomodulation therapy.

Supplementary material. The supplementary material for this article can be found at [https://doi.org/10.1017/S0022215123002165].

Competing interests. None declared

References

1 Heller AJ. Classification and epidemiology of tinnitus. *Otolaryngol Clin North Am* 2003;**36**:239–48
2 Han BI, Lee HW, Kim TY, Lim JS, Shin KS. Tinnitus: characteristics, causes, mechanisms, and treatments. *J Clin Neurol* 2009;**5**:11–19
3 Stockdale D, McFerran D, Brazier P, Pritchard C, Kay T, Dowrick C, Hoare DJ. An economic evaluation of the healthcare cost of tinnitus management in the UK. *BMC Health Serv Res* **17**:577
4 Bhatt JM, Lin HW, Bhattacharyya N. Tinnitus epidemiology: prevalence, severity, exposures and treatment patterns in the United States. *JAMA Otolaryngol Head Neck Surg* 2016;**142**:959–65
5 Langguth B, Salvi R, Elgoyhen AB. Emerging pharmocotherapy of tinnitus. *Expert Opin Emerg Drugs* 2009;**14**:687–702
6 Kapkin O, Satar B, Yetiser S. Transcutaneous electrical stimulation of subjective tinnitus. A placebo-controlled, randomized and comparative analysis. *ORL J Otorhinolaryngol Relat Spec* 2008;**70**:156–61
7 Soleymani T, Pieton D, Pezeshkian P, Miller P, Gorgulho AA, Pouratian N *et al.* Surgical approaches to tinnitus treatment: a review and novel approaches. *Surg Neurol Int* 2011;**2**:154
8 Dompe C, Moncrieff L, Matys J, Grzech-Leśniak K, Kocherova I, Bryja A *et al.* Photobiomodulation-underlying mechanism and clinical applications. *J Clin Med* 2020;**9**:1724
9 Wong-Riley MTT, Liang HL, Eells JT, Chance B, Henry MM, Buchmann E *et al.* Photobiomodulation directly benefits primary neurons functionally inactivated by toxins: role of cytochrome c oxidase. *J Biol Chem* 2005;**280**:4761–71
10 Huang Y-Y, Chen AC-H, Carroll JD, Hamblin MR. Biphasic dose response in low level light therapy. *Dose Response* 2009;**7**:358–83
11 Oron U, Ilic S, De Taboada L, Streeter J. Ga-As (808 nm) laser irradiation enhances ATP production in human neuronal cells in culture. *Photomed Laser Surg* 2007;**25**:180–2
12 Wilden L, Dindinger D. Treatment of chronic diseases of the inner ear with low level laser therapy (LLLT): pilot project. *Laser Ther* 1996;**8**:209–12
13 Dejakum K, Piegger J, Plewka C, Gunkel A, Thumfart W, Kudaibergenova S *et al.* Medium-level laser in chronic tinnitus treatment. *Biomed Res Int* 2013;**2013**:324234
14 Choi JE, Lee MY, Chung P-S, Jung JY. A preliminary study on the efficacy and safety of low level light therapy in the management of cochlear tinnitus: a single blind randomized clinical trial. *Int Tinnitus J* 2019;**23**:52–7
15 Talluri S, Palaparthi SM, Michelogiannakis D, Khan J. Efficacy of photobiomodulation in the management of tinnitus: a systematic review of randomized control trials. *Eur Ann Otorhinolaryngol Head Neck Dis* 2022;**139**:83–90

16 Page MJ, McKenzie JE, Bossuyt PM, Bourton I, Hoffman TC, Murlow CD *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;**372**:n71
17 Hooijmans CR, Rovers MM, de Vries RBM, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. *BMC Med Res Methodol* 2014;**14**:43
18 Oxford Centre for Evidence-based Medicine - Levels of Evidence (March 2009). In: https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/ [28 January 2024]
19 Cochrane. Risk of Bias 2 (RoB 2) tool. In: https://methods.cochrane.org/risk-bias-2 [28 January 2024]
20 Brazzelli M, Cruickshank M, Tassie E, McNamee P, Robertson C, Elders A *et al.* Collagenase clostridium histolyticum for the treatment of Dupuytren's contracture: systematic review and economic evaluation. 2015 Appendix 5. In: https://www.ncbi.nlm.nih.gov/books/NBK326583 [28 January 2024]
21 Rhee C-K, Lim E-S, Kim Y-S, Chung Y-W, Jung J-Y, Chung P-S. Effect of low level laser (LLL) on cochlear and vestibular inner ear including tinnitus. *SPIE BiOS* 2006;**6078**:268–79
22 Park YM, Na WS, Park IY, Suh M-W, Rhee C-K, Chung P-S *et al.* Trans-canal laser irradiation reduces tinnitus perception of salicylate treated rat. *Neurosci Lett* 2013;**544**:131–5
23 Mirz F, Zachariae R, Andersen SE, Nielsen AG, Johansen LV, Bjerring P *et al.* The low-power laser in the treatment of tinnitus. *Clin Otolaryngol* 1999;**24**:346–54
24 Mirvakili A, Mehrparvar A, Mostaghaci M, Mollasadeghi A, Mirvakili M, Baradaranfar M *et al.* Low level laser effect in treatment of patients with intractable tinnitus due to sensorineural hearing loss. *J Lasers Med Sci* 2014;**5**:71–4
25 Mollasadeghi A, Mirmohammadi SJ, Mehrparvar AH, Davari MH, Shokouh P, Mostaghaci M *et al.* Efficacy of low-level laser therapy in the management of tinnitus due to noise-induced hearing loss: a double-blind randomized clinical trial. *ScientificWorldJournal* 2013;**2013**:596076
26 Yildirim G, Berkiten G, Ugras H, Salturk Z. Changes in audiometry results following laser therapy for tinnitus. *Eur J Gen Med* 2011;**8**:284–90
27 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* 2003;**18**:154–61
28 Okhovat A, Berjis N, Okhovat H, Malekpour A, Abtahi H. Low-level laser for treatment of tinnitus: a self-controlled clinical trial. *J Res Med Sci* 2011;**16**:33–8
29 Demirkol N, Usumez A, Demirkol M, Sari F, Akcaboy C. Efficacy of low-level laser therapy in subjective tinnitus patients with temporomandibular disorders. *Photomed Laser Surg* 2017;**35**:427–31
30 Gungor A, Dogru S, Cincik H, Erkul E, Poyrazoglu E. Effectiveness of transmeatal low power laser irradiation for chronic tinnitus. *J Laryngol Otol* 2008;**122**:447–51
31 Toson RAM, Khalaf MM, Seleim AM, Hassan MA. Treatment of chronic tinnitus with low level laser therapy. *Int J PharmTech Res* 2016;**9**:37–45
32 Elsayed OA, Alsharif B. Low-level laser therapy for treatment of tinnitus in Red Sea scuba divers: a randomized clinical study. *Egypt J Otolaryngol* 2022;**38**:4
33 Eladl HM, Elkholi SM, Eid MM, Abdelbasset WK, Ali ZA, Bahey El-Deen HA. Effect of adding a supervised physical therapy exercise program to photobiomodulation therapy in the treatment of cervicogenic somatosensory tinnitus: a randomized controlled study. *Medicine (Baltimore)* 2022;**101**:e29946
34 Elsanadiky HH, Nafie Y. Evaluation of transient evoked otoacoustic emissions using low-level laser stimulation in individuals with normal hearing with tinnitus. *Tanta Med J* 2017;**45**:45–50
35 Ngao CF, Tan TS, Narayanan P, Raman R. The effectiveness of transmeatal low-power laser stimulation in treating tinnitus. *Eur Arch Otorhinolaryngol* 2014;**271**:975–80
36 Nakashima T, Ueda H, Misawa H, Suzuki T, Tominaga M, Ito A *et al.* Transmeatal low-power laser irradiation for tinnitus. *Otol Neurotol* 2002;**23**:296–300
37 Teggi R, Bellini C, Piccioni LO, Palonta F, Bussi M. Transmeatal low-level laser therapy for chronic tinnitus with cochlear dysfunction. *Audiol Neurootol* 2009;**14**:115–20
38 Salahaldin AH, Abdulhadi K, Najjar N, Bener A. Low-level laser therapy in patients with complaints of tinnitus: a clinical study. *ISRN Otolaryngol* 2012;**2012**:132060
39 Plath P, Olivier J. Results of combined low-power laser therapy and extracts of Ginkgo biloba in cases of sensorineural hearing loss and tinnitus. *Adv Otorhinolaryngol* 1995;**49**:101–4
40 Montazeri K, Mahmoudian S, Razaghi Z, Farhadi M. Alterations in auditory electrophysiological responses associated with temporary suppression of tinnitus induced by low-level laser therapy: a before-after case series. *J Lasers Med Sci* 2017;**8**:S38–45
41 Thabit MN, Fouad N, Shahat B, Youssif M. Combined central and peripheral stimulation for treatment of chronic tinnitus: a randomized pilot study. *Neurorehabil Neural Repair* 2015;**29**:224–33
42 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**:39–42
43 Silva MR, Scheffer AR, Bastos RSA, Chavantes MC, Mondelli MFCG. The effects of photobiomodulation therapy in individuals with tinnitus and without hearing loss. *Lasers Med Sci* 2022;**37**:3485–94
44 Cuda D, De Caria A. Effectiveness of combined counseling and low-level laser stimulation in the treatment of disturbing chronic tinnitus. *Int Tinnitus J* 2008;**14**:175–80
45 Beyer W, Baumgartner R, Tauber S. Dosimetric analysis for low-level-laser therapy (LLLT) of the human inner ear at 593nm and 633nm. *Proc SPIE* 1998;**3569**:56–9
46 Sommer AP, Pinheiro AL, Mester AR, Franke RP, Whelan HT. Biostimulatory windows in low-intensity laser activation: lasers, scanners, and NASA's light-emitting diode array system. *J Clin Laser Med Surg* 2001;**19**:29–33
47 Rhee C-K, He P, Jung JY, Ahn J-C, Chung P-S, Suh M-W. Effect of low-level laser therapy on cochlear hair cell recovery after gentamicin-induced ototoxicity. *Lasers Med Sci* 2012;**27**:987–92