National Institute for Health and Care Excellence

Final

Tinnitus: assessment and management

[O] Evidence review for neuromodulation

NICE guideline NG155

Intervention evidence review

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Final

This evidence review was developed by the National Guideline Centre

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1.1 Review question: What is the clinical and cost effectiveness of neuromodulation for people with tinnitus?

1.2 Introduction

A number of physiological mechanisms for tinnitus have been proposed. One of these proposed mechanisms is that the perception of tinnitus is caused by abnormal synchronisation of neural activity in the central auditory nervous system. Neuromodulation aims to normalise neural activity of the auditory system, thereby reducing the perception of tinnitus.

There are a variety of methods which report to use a neuromodulation approach. Neuromodulation therapies may involve the application of electrical, acoustic and/or magnetic energy to the head or neck to alleviate the tinnitus symptoms. None are currently available on the National Health Service.

The aim of this review question is to examine the evidence to determine whether neuromodulation is a clinically and cost effective treatment for people with tinnitus.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	Children, young people and adults with tinnitus. Strata: children/young people and adults
Interventions	Neuromodulation interventions: • transcranial direct current stimulation (tDCS) • transcranial alternating current stimulation (tACS) • vagal nerve stimulation (VNS) • transcutaneous vagal nerve stimulation (tVNS) • acoustic neuromodulation therapy • paired electrical and acoustic stimulation therapy • repetitive transcranial magnetic stimulation (rTMS)
Comparisons	• Interventions compared with each other • Control group (no intervention, sham intervention or waiting-list control) • **Sound therapy and sound enrichment** o sound enrichment (e.g. environmental sound, a CD or mp3 download or the radio, a smartphone App, bedside/table-top sound generators, a wearable sound generator) o Customised sound-based therapies, e.g. amplitude modulated tones and notched noise/music o Masking • **Amplification devices for people with hearing loss** o Hearing aids o Implantable devices (including cochlear implants, bone-anchored hearing aids, bone-conduction hearing implants, bone-bridge/middle-ear devices)

	• Combination device (sound generator and hearing aids) • Tinnitus education including coping strategies, provision of information and advice and relaxation
Outcomes	• Tinnitus severity (critical) Impact of tinnitus (critical): • Tinnitus distress • Tinnitus annoyance Health related QoL (critical): • QoL (tinnitus) • QoL Tinnitus percept (important): • Tinnitus loudness Other co-occurring complaints (important): • Depression • Anxiety • Anxiety and depression • Sleep Adverse events (important) • Safety • Tolerability/adherence/drop-outs/attrition • Side effects (e.g. worsening of tinnitus)
Study design	• Systematic review of RCTs • RCT • If there is an inadequate amount of RCT data, non-randomised comparative studies will be considered.

1.4 Clinical evidence

1.4.1 Included studies

Sixteen studies were included in the review; [2, 3, 5, 9-11, 14, 24, 25, 29, 35, 42, 44, 47, 51, 58] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix H.

1.4.2 Excluded studies

One Cochrane systematic review [31] was identified, which assesses rTMS for tinnitus, but was not included because multiple included studies only reported outcomes that the committee agreed are not relevant for this review, including 'response to treatment'. This Cochrane review was screened and three eligible studies[2, 14, 29] were included in this review.

See the excluded studies list in appendix I.

1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Anders 2010[2] RCT	Intervention (n=26): rTMS (1 Hz) Number of sessions: 5 sessions over 5 days Duration of sessions not stated. Further details: sham rTMS was delivered through a figure-eight coil. The stimulation intensity was 110% of the individual's resting motor threshold, with 1500 stimuli per session and coil positioned over the left primary auditory cortex. Comparison (n=26): Sham rTMS Number of sessions: 5 sessions over 5 days Duration of sessions not stated. Further details: Sham stimulation was carried out by tilting the coil 45 degrees away from the skull.	n=52 People with chronic tinnitus Age, mean (SD): rTMS group 48.09 (12.86) sham group 50.05 (13.97) years 29 male, 13 female Duration of tinnitus: at least 6 months Czech Republic	Tinnitus severity (Tinnitus Handicap Inventory 0-100) (post-treatment and 6 month follow-up Tinnitus severity (Tinnitus Questionnaire 0-100) (post-treatment and 6 month follow-up)	
Bilici 2015[3] RCT	Intervention 1 (n=15): rTMS (1 Hz) Number of sessions: 10 sessions over 10 days Duration of sessions: 15 min.	n=75 People with chronic tinnitus Age, mean (SD): 40	Tinnitus severity (Tinnitus Handicap Inventory 0-100) (post-treatment and 6 month follow-up) Tinnitus severity (Tinnitus	Note: this study included two other intervention arms featuring selective serotonin uptake

Study	Intervention and comparison	Population	Outcomes	Comments
	Further details: A neuro-MS magnetic stimulator with a large circular coil was used. 900 stimuli were applied at an intensity of 110% resting motor threshold. Stimulation was applied via a coil placed close to the left temporoparietal region, independent of the side of the tinnitus. Intervention 2 (n=15): rTMS (10 Hz) Number of sessions: 10 sessions over 10 days Duration of sessions: 15 mins Further details: 600 stimuli were applied as 20 trains of 30 stimuli (inter-train interval of 25 seconds) at an intensity of 110% resting motor threshold. Comparison (n=15): Sham rTMS Further details: Placebo stimulation was performed with a sham coil system that mimicked the sound of active stimulation, without producing a magnetic field.	(13.2) years 33 male, 42 female Duration of tinnitus: at least 1 year Turkey	Severity Index 0-100) (post-treatment and 6 month follow-up) Anxiety (Beck Anxiety Inventory 0-63) (post-treatment and 6 month follow-up)	inhibitors (SSRIs) (both n=15) which were not suitable for inclusion here but contribute to the total number of study participants.
Chung 2012[5] RCT	Intervention (n=12): rTMS (1 Hz) Number of sessions: 10 sessions over 10 days Further details: TMS was applied using a figure-eight-shaped coil (Magstim	n=22 People with chronic tinnitus Age, mean (SD): Active rTMS group 53.83 (18.4)	Tinnitus severity (Tinnitus Handicap Inventory 0-100) (post-treatment and 1 month follow-up) Tinnitus severity (Tinnitus Questionnaire 0-100) (post-	

Study	Intervention and comparison	Population	Outcomes	Comments
	SuperRapid). Comparison (n=10): Sham rTMS Number of sessions: 10 sessions over 10 days. Further details: the sham stimulation group patients received an identical protocol to the active-stimulation group, but with the sham coil (Magstim).	Sham rTMS group 51.9 (15.5) years 20 male, 2 female Duration of tinnitus: unclear China	treatment and 1 month follow-up)	
Folmer 2015[9] RCT	Intervention (n=35): rTMS (1 Hz) Number of sessions: 10 sessions over 10 days. Further details: Subjects received 2000 pulses of active rTMS at a rate of 1 Hz and stimulation intensity of110% of the individual resting motor threshold or lower, with the figure-of-eight coil positioned over left auditory cortex. Comparison (n=35): Sham rTMS Number of sessions: 10 sessions over 10 days. Further details: The placebo coil (Magstim) was identical in appearance to the active coil and produced sounds and scalp sensations that were similar to those produced by the active coil.	n=70 People with chronic tinnitus Age, mean (SD): 60.6 (8.9) years 51 male, 13 female Duration of tinnitus: At least 1 year USA	Tinnitus severity (Tinnitus Functional Index 0-100) (post-treatment and 6 month follow-up)	

Study	Intervention and comparison	Population	Outcomes	Comments
Formanek 2018[10] RCT	Intervention (n=20): rTMS (1 Hz + 25 Hz combined) Number of sessions: 5 sessions over 5 days Duration of sessions not stated. Further details: rTMS was performed with a 70-mm air-cooled 70BF Butterfly Coil (Deymed). The dorsolateral prefrontal cortex (frequency 25 Hz, 300 pulses, and 80% RMT) on the left side and primary auditory cortex on both sides (1 Hz,1000 pulses, and 110% RMT) were stimulated. Every patient received 2300 pulses per session (three stimulation sites). Comparison (n=12) Sham rTMS Number of sessions: 5 sessions over 5 days Duration of sessions not stated. Further details: Placebo treatment was performed with a 70-mm 70BFP Placebo Butterfly Coil (Deymed) replicating the appearance, sound emission, stimulation of superficial tissue (muscles), and operation of the TMS coil without stimulating the cortical tissue.	n=32 People with tinnitus Age, mean (SD): rTMS group 47.9 (14.31) sham group 51.8 (10.34) years 23 male, 9 female Duration of tinnitus in months, mean (SD): rTMS group 53.4 (61.89), sham group 76.8 (76.85) Czech Republic	Tinnitus severity (Tinnitus Handicap Inventory 0-100) (post-treatment and 6 months follow-up) Tinnitus severity (Tinnitus Handicap Questionnaire 0-100) (post-treatment and 6 month follow-up) Depression (Beck Depression Inventory 0-63) (post-treatment and 6 months follow-up)	
Forogh 2016[11] RCT	Intervention (n=11): tDCS	n=22 People with chronic	Tinnitus severity (Tinnitus Handicap Inventory 0-100) (post-treatment and 2 week	

Study	Intervention and comparison	Population	Outcomes	Comments
	Left temporal area (LTA) Number of sessions: 5 sessions over 5 days. Duration of sessions: 20 mins. Further details: The anode electrode was positioned over left temporoparietal area and the cathode electrode was placed over right supraorbital area. Direct electrical current was generated by a battery-driven direct current stimulator (Activadose II). Comparison (n=11): Sham tDCS Number of sessions: 5 sessions over 5 days. Duration of sessions: 20 mins. Further details: In the sham group, after the initial ramp-up the current was directly ramped down to 9, so patients felt a tingling sensation at the beginning and received no more stimulation in the remaining time of the session.	tinnitus Age, mean (range): 48.22 (26-80) years 14 male, 8 female Duration of tinnitus: at least 6 months Iran	follow-up) Tinnitus distress (on VAS 0-10) (post-treatment and 2 week follow-up) Tinnitus loudness (on VAS 0-10) (post-treatment and 2 week follow-up)	
Ghossaini 2004[14] RCT	Intervention (n=18): rTMS (27 MHz) Number of sessions: 12 (3 per week for 1 month) Duration of sessions: 30 minutes Further details: A Diapulse device (model D103) produced pulsed electromagnetic energy at a frequency of 27.12 MHz in 65-	n=37 People with chronic tinnitus Age range: 23 – 83 years. Genders not stated.	Tinnitus severity (Tinnitus Handicap Inventory 0-100) (post-treatment) Tinnitus severity (Tinnitus Magnitude Rating 0-100) (post-treatment) Adverse events: worsening of	

Study	Intervention and comparison	Population	Outcomes	Comments
	microsecond bursts with a repetition rate of 600 pulses per second at 975 W peak and a 6-inch penetration depth. Patients with bilateral tinnitus received treatment to the ear with louder tinnitus. Comparison (n=19): Sham rTMS Number of sessions: 12 (3 per week for 1 month) Duration of sessions: 30 minutes Further details: Patients in the placebo group were treated with a deactivated rTMS machine. The active treatment device emits non-thermal energy and so cannot be felt. Both active and placebo machines were identical in appearance, sound and presence of light when active.	Duration of tinnitus ranged from 7 months to 60 years. USA	tinnitus (post-treatment)	
Landgrebe 2017[24] RCT	Intervention (n=75): rTMS (1 Hz) Number of sessions: 10 sessions over 10 days. Further details: Using a MagPro X-100 or MagPro R30 TMS stimulator with figure-of-eight coil. 2000 stimuli per session were applied to the left primary auditory cortex with a stimulation intensity of 110% related to the individual resting motor threshold. Comparison (n=78):	n=153 People with chronic tinnitus Age, mean (SD): Real rTMS group 48.1 (12.5) Sham rTMS group 49.9 (13.2) years 105 male, 41 female Duration of tinnitus: at least 6 months	Tinnitus severity (Tinnitus Handicap Inventory 0-100) (post-treatment and 6 month follow-up) Tinnitus severity (Tinnitus Questionnaire 0-100) (post-treatment and 6 month follow-up) Health related quality of life (SF-12 Physical component 0-100) (post-treatment and 6 month follow-up)	

Study	Intervention and comparison	Population	Outcomes	Comments
	Sham rTMS Number of sessions: 10 sessions over 10 days. Further details: Patients in the sham group received the same treatment but the stimulation coil was tilted away from the skull by 45 degrees with one wing touching the skull.	Germany	Health related quality of life (SF-12 Mental component 0-100) (post-treatment and 6 month follow-up) Depression (Beck Depression Inventory 0-63) (post-treatment and 6 month follow up)	
Langguth 2014[25] RCT	Intervention (n=48): rTMS (1 Hz) PET-guided, neuronavigated Number of sessions: 10 sessions over 10 days. Further details: FDG-PET and MRI were used to identify the area of increased activation within the auditory cortices and rTMS applied with a figure-of-eight coil connected to a stimulator, with 2000 stimuli per session at a frequency of 1 Hz and an intensity of 110% motor threshold. Comparison (n=48): Sham rTMS Number of sessions: 10 sessions over 10 days. Further details: For sham stimulation, a specific sham-coil system was used (MC-B70 Medtronic).	n=96 People with chronic tinnitus Age, mean (SD): Active group 44.9 (11.5) sham group 50.3 (12.9) years 65 male, 27 female (analysed) Duration of tinnitus: at least 3 months. Germany	Tinnitus severity (Tinnitus Questionnaire 0-100) (post-treatment)	
Marcondes 2010[29]	Intervention (n=10):	n=19	Tinnitus severity (Tinnitus Handicap Inventory 0-100)	

Study	Intervention and comparison	Population	Outcomes	Comments
RCT	rTMS (1 Hz) Number of sessions: 5 sessions over 5 days. Duration of sessions: 17 mins. Further details: 1020 stimuli were administered with an intensity of 110% motor threshold at a frequency of 1 Hz over the left temporoparietal cortex. Comparison (n=9): Sham rTMS Number of sessions: 5 sessions over 5 days. Duration of sessions: 17 mins. Further details: Placebo stimulation was performed with a sham coil system which mimics the sound of active stimulation, without producing a magnetic field.	People with chronic tinnitus Age: over 18 years Gender ratio not reported. Duration of tinnitus: at least 3 months Brazil	(post-treatment and 3 month follow-up)	
Pal 2015[35] RCT	Intervention (n=21): tDCS Right dorsolateral prefrontal cortex (DLPFC) Number of sessions: 5 sessions over 5 days. Duration of sessions: 20 mins. Further details: Electrodes were positioned using the International 10-20 EEG system. Direct current was transmitted by saline-soaked surface sponges that came with the CE-certified battery-driven constant current stimulator	n=42 People with chronic tinnitus Age, mean (SD): tDCS group 51.6 (12.2) sham group 48 (9.9) years 24 male, 18 female	Tinnitus severity (Tinnitus Handicap Inventory 0-100) (post-treatment and 3 month follow-up) Tinnitus severity (Subjective Tinnitus Severity Scale 0-100) (post-treatment and 3 month follow-up) Tinnitus severity (tinnitus intensity on VAS 0-100) (post-treatment and 3 month follow-	

Study	Intervention and comparison	Population	Outcomes	Comments
	(BrainSTIM Transcranial Stimulator). Comparison (n=21): Sham tDCS Number of sessions: 5 sessions over 5 days. Duration of sessions: 20 mins. Further details: For sham stimulation a small anode and cathode were placed 1 cm apart over the forehead to mimic the position of F3-Fz-F4, and two inactive electrodes placed at T3 and T4.	Duration of tinnitus: at least 1 year Switzerland	up) Tinnitus severity (Clinical Global Impression Scale 0-100) (post-treatment and 3 month follow-up) Tinnitus distress (VAS 0-100) (post-treatment and 3 month follow-up) Anxiety and depression (Hospital Anxiety and Depression Scale 0-21) (1 month follow-up)	
Sahlsten 2017[42] RCT	Intervention (n=22): rTMS (1 Hz) Number of sessions: 10 treatments over 10 days. Further details: Each session consisted of 4000 pulses at a continuous 1 Hz rate given to the left superior temporal gyrus (STG) at 100% of the RMT. Comparison (n=20): Sham rTMS Number of sessions: 10 treatments over 10 days. Further details: For placebo stimulation, a 15-cm plastic block was attached to the coil without the patient seeing it. The	n=42 People with chronic tinnitus Age, mean (SD): rTMS group 48.9 (13.1) Sham group 51.5 (10.7) years 27 male, 12 female Duration of tinnitus: 6 months to 10 years Finland	Tinnitus severity (tinnitus intensity on VAS 0-100) (post-treatment and 3 month follow-up) Tinnitus distress (VAS 0-100) (post-treatment and 3 month follow-up) Tinnitus annoyance (VAS 0-100) (post-treatment and 3 month follow-up)	

Study	Intervention and comparison	Population	Outcomes	Comments
	added distance effectively lowered the E-field to the cortex to negligible amounts of 1-4 V/m. All patients wore earplugs.			
Shekhawat 2018[44] RCT	Intervention (n=6): tDCS Right dorsolateral prefrontal cortex (DLPFC) Number of sessions: 1 Duration of sessions: 20 mins. Further details: A NeuroConn DC stimulator was used for all procedures. A 4 x 1 HD-tDCS was placed on the scalp with the central electrode (anode) placed on the right dorsolateral prefrontal cortex. Comparison (n=7): Sham tDCS Number of sessions: 1 Duration of sessions: 20 mins Further details: Sham stimulation included only the 30 second fade-in/out and there was no stimulation in between the fade in and fade out periods.	n=13 People with chronic tinnitus Age, mean: 53.6 years All male Duration of tinnitus: at least 2 years New Zealand	Tinnitus annoyance (on VAS 0-100) (post-treatment) Tinnitus loudness (on VAS 0-100) (post-treatment)	
Tass 2012[47] RCT	Intervention (n=58): Acoustic CR neurostimulation Details: There were 4 active treatment groups, G1,G2,G3,G4, which all received different tone frequencies of treatment	n= 63 People with chronic tinnitus Age, mean (SD):	Tinnitus severity (Tinnitus Questionnaire 0-100) (post-treatment and 4 week follow-up) Tinnitus annoyance (on VAS	Participants were randomised into different doses/frequencies of acoustic CR neurostimulation. Results were combined

Study	Intervention and comparison	Population	Outcomes	Comments
	(pooled for this analysis). G1 to G3 all received stimulation for 4–6hours every day, applied either continuously or split into several sessions not shorter than 1 hour each to utilize cumulative effects. G4 received stimulation for 1 hour max every day. Stimulation signals were generated based on a specific formula reflecting the logarithmic tonotopic organization of the auditory cortex and on the matched tinnitus with an equal number of tones placed below and above tinnitus frequency. Comparison (n=5): Sham The control group, G5, was based on a modified tinnitus frequency. Stimulation tones in the placebo group were administered at a calculated frequency below the patient's tinnitus frequency	G1 45.7 (10.8) ; G2 47.7 (5.6) ; G3 50.0 (14.7) ; G4 50.3 (11.8), G5(control) 57.6 (6.3) years Percentage male: G1 - 72.7%; G2 - 83.3%; G3 - 50%; G4 - 75% ; G5 (control) – 60% Duration of tinnitus: At least 6 months Germany	0-100) (post-treatment and 4 week follow-up) Tinnitus loudness (on VAS 0-100) (post-treatment and 4 week follow-up)	for the groups.
Tyler 2017[51] RCT	Intervention (n=16): Vagal nerve stimulation (VNS) Number and duration of sessions: Participants performed the treatment at home for approximately 2.5 hours/day, 7 days/week for 6 weeks. Further details: The VNS device was implanted with the lead's stimulation electrodes placed on the left vagus nerve in the carotid sheath. The device consisted of an implantable pulse	n=30 People with chronic tinnitus Age, mean (SD): VNS group 55.9 (7.6) Control group 54.9 (9.1) years 25 male, 5 female	Tinnitus severity (Tinnitus Handicap Inventory 0-100) (post-treatment) Tinnitus severity (Tinnitus Handicap Questionnaire 0-100) (post-treatment) Tinnitus severity (Tinnitus Functional Index 0-100) (post-treatment)	

Study	Intervention and comparison	Population	Outcomes	Comments
	generator (Model 1000 Serenity), an implantable lead and electrode (Model 3000), and an external controller system. Each VNS stimulation consisted of fifteen 0.8 mA, constant current, charge balanced pulses (100 μs pulse width, at 30 Hz). Comparison (n=14): Sham VNS In the control (unpaired) group, VNS was not paired with tones (10 minutes of tones only, 5 minutes of silence and no VNS; 2 hours of VNS only; 5 minutes of silence and no VNS, and 10 minutes of tones only) during the 2.5-hour period.	Duration of tinnitus: unclear USA	Tinnitus loudness (on VAS 0-100) (post-treatment)	
Yilmaz 2014[58] RCT	Intervention (n=30): rTMS (1 Hz) Number of sessions: 10 sessions over 10 days. Duration of sessions: 30 mins. Further details: Treatment was performed using a Neuro-MS TMS device and a figure-of-eight coil. Comparison (n=30): Sham rTMS Number of sessions: 10 sessions over 10 days. Duration of sessions: 30 mins.	n=60 People with chronic tinnitus Age, mean (SD): 49.5 (8.03) years Gender ratio not reported. Duration of tinnitus: at least 6 months. Turkey	Tinnitus severity (Tinnitus Handicap Inventory 0-100) (1 month follow-up) Tinnitus loudness (on VAS 0-100) (1 month follow-up)	

Study	Intervention and comparison	Population	Outcomes	Comments
	Further details: not given.			

See appendix D for full evidence tables.

1.4.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: rTMS (1 Hz) (low frequency) versus sham rTMS

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Sham rTMS	Risk difference with rTMS (1 Hz) (low frequency) (95% CI)
Tinnitus severity (Tinnitus Handicap Inventory) Scale from: 0 to 100.	259 (5 studies) Post-treatment	⨁⊖⊖⊖ VERY LOW2,3,4 due to risk of bias, inconsistency, imprecision		The mean tinnitus severity in the control groups was 28.9 1	The mean tinnitus severity in the intervention groups was 5.14 lower (13.41 to 3.14 higher)
Tinnitus severity (Tinnitus Handicap Inventory) Scale from: 0 to 100.	304 (6 studies) 1 to 9 months	⨁⨁⊖⊖ LOW2 due to risk of bias		The mean tinnitus severity in the control groups was 38.35 1	The mean tinnitus severity in the intervention groups was 5.45 lower (8.87 to 2.03 lower)
Tinnitus severity (Tinnitus Questionnaire) Scale from: 0 to 100.	301 (4 studies) Post-treatment	⨁⊖⊖⊖ VERY LOW2,3,4 due to risk of bias, inconsistency, imprecision		The mean tinnitus severity in the control groups was 31.63 1	The mean tinnitus severity in the intervention groups was 0.86 lower (6.36 lower to 4.64 higher)
Tinnitus severity (Tinnitus Questionnaire) Scale from: 0 to 100.	194 (3 studies) 1 to 6 months	⨁⊖⊖⊖ VERY LOW2,3 due to risk of bias, inconsistency		The mean tinnitus severity in the control groups was 32.9 1	The mean tinnitus severity in the intervention groups was 2.75 lower (8.1 lower to 2.6 higher)
Tinnitus severity (Tinnitus Severity Index)	30 (1 study)	⨁⊖⊖⊖ VERY LOW2,4 due to risk of bias,		The mean tinnitus severity (Tinnitus Severity Index) (post-treatment) in the control groups was	The mean tinnitus severity in the intervention groups was 3.7 lower

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Sham rTMS	Risk difference with rTMS (1 Hz) (low frequency) (95% CI)
Scale from: 0 to 100.	Post-treatment	imprecision		-0.6 change score	(7.9 lower to 0.5 higher)
Tinnitus severity (Tinnitus Severity Index) Scale from: 0 to 100.	30 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW2,4 due to risk of bias, imprecision		The mean tinnitus severity in the control groups was 1.1 change score	The mean tinnitus severity in the intervention groups was 4.8 lower (11.39 lower to 1.79 higher)
Tinnitus severity (Tinnitus Functional Index) Scale from: 0 to 100.	64 (1 study) Post-treatment	⨁⨁⨁⊖ MODERATE4 due to imprecision		The mean tinnitus severity in the control groups was -1.8 change score	The mean tinnitus severity in the intervention groups was 3.4 lower (8.87 lower to 2.07 higher)
Tinnitus severity (Tinnitus Functional Index) Scale from: 0 to 100.	64 (1 study) 6 months	⨁⨁⨁⊖ MODERATE4 due to imprecision		The mean tinnitus severity in the control groups was -2.9 change score	The mean tinnitus severity in the intervention groups was 10.9 lower (18.5 to 3.3 lower)
Tinnitus severity (tinnitus intensity on VAS) Scale from: 0 to 100.	39 (1 study) Post-treatment	⨁⊖⊖⊖ VERY LOW2,4 due to risk of bias, imprecision		The mean tinnitus severity in the control groups was 50.6	The mean tinnitus severity in the intervention groups was 15.1 lower (30.37 lower to 0.17 higher)
Tinnitus severity (tinnitus intensity on VAS) Scale from: 0 to 100.	39 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW2,4 due to risk of bias, imprecision		The mean tinnitus severity in the control groups was 50.3	The mean tinnitus severity in the intervention groups was 11.8 lower (28.18 lower to 4.58 higher)
Health related quality of life (SF-12 Physical component) Scale from: 0 to 100.	146 (1 study) Post-treatment	⨁⨁⨁⨁ HIGH		The mean health related quality of life in the control groups was 47.5	The mean health related quality of life in the intervention groups was 0.3 higher (2.26 lower to 2.86 higher)
Health related quality of life (SF-12 Physical component) Scale from: 0 to 100.	111 (1 study) 6 months	⨁⨁⊖⊖ LOW2 due to risk of bias		The mean health related quality of life in the control groups was 46.6	The mean health related quality of life in the intervention groups was 0.3 higher (3.13 lower to 3.73 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Sham rTMS	Risk difference with rTMS (1 Hz) (low frequency) (95% CI)
Health related quality of life (SF-12 Mental component) Scale from: 0 to 100.	146 (1 study) Post-treatment	⨁⨁⨁⨁ HIGH		The mean health related quality of life in the control groups was 48.1	The mean health related quality of life in the intervention groups was 1 lower (4.38 lower to 2.38 higher)
Health related quality of life (SF-12 Mental component) Scale from: 0 to 100.	111 (1 study) 6 months	⨁⨁⨀⨀ LOW2 due to risk of bias		The mean health related quality of life in the control groups was 47.1	The mean health related quality of life in the intervention groups was 0.5 lower (4.73 lower to 3.73 higher)
Tinnitus distress (VAS) Scale from: 0 to 100.	39 (1 study) Post-treatment	⨁⨀⨀⨀ VERY LOW2,4 due to risk of bias, imprecision		The mean tinnitus distress in the control groups was 43.2	The mean tinnitus distress in the intervention groups was 8.3 lower (22.88 lower to 6.28 higher)
Tinnitus distress (VAS) Scale from: 0 to 100.	39 (1 study) 3 months	⨁⨀⨀⨀ VERY LOW2,4 due to risk of bias, imprecision		The mean tinnitus distress in the control groups was 48.5	The mean tinnitus distress in the intervention groups was 9.2 lower (25.3 lower to 6.9 higher)
Tinnitus annoyance (VAS) Scale from: 0 to 100.	39 (1 study) Post-treatment	⨁⨀⨀⨀ VERY LOW2,4 due to risk of bias, imprecision		The mean tinnitus annoyance in the control groups was 43.2	The mean tinnitus annoyance in the intervention groups was 6.7 lower (21.28 lower to 7.88 higher)
Tinnitus annoyance (VAS) Scale from: 0 to 100.	39 (1 study) 3 months	⨁⨀⨀⨀ VERY LOW2,4 due to risk of bias, imprecision		The mean tinnitus annoyance in the control groups was 46.1	The mean tinnitus annoyance in the intervention groups was 6.5 lower (22.6 lower to 9.6 higher)
Anxiety (Beck Anxiety Inventory) Scale from: 0 to 63.	30 (1 study) Post-treatment	⨁⨀⨀⨀ VERY LOW2,4 due to risk of bias, imprecision		The mean anxiety in the control groups was 13.0	The mean anxiety in the intervention groups was 2.5 lower (9.12 lower to 4.12 higher)
Anxiety (Beck Anxiety Inventory)	30 (1 study)	⨁⨀⨀⨀ VERY LOW2,4		The mean anxiety in the control groups was	The mean anxiety in the intervention groups was

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Sham rTMS	Risk difference with rTMS (1 Hz) (low frequency) (95% CI)
Scale from: 0 to 63.	6 months	due to risk of bias, imprecision		14.1	3.8 lower (10.45 lower to 2.85 higher)
Depression (Beck Depression Inventory) Scale from: 0 to 63.	146 (1 study) Post-treatment	⊕⊕⊕⊕ HIGH		The mean depression in the control groups was 7.7	The mean depression in the intervention groups was 0.4 higher (1.63 lower to 2.43 higher)
Depression (Beck Depression Inventory) Scale from: 0 to 63.	146 (1 study) 6 months	⊕⊕⊖⊖ LOW2 due to risk of bias		The mean depression in the control groups was 8.2	The mean depression in the intervention groups was 0.6 higher (2.15 lower to 3.35 higher)
Tinnitus loudness Scale from: 0 to 100.	60 (1 study) 1 month	⊕⊖⊖⊖ VERY LOW2,4 due to risk of bias, imprecision		The mean tinnitus loudness in the control groups was 50.61	The mean tinnitus loudness in the intervention groups was 0.52 lower (7.34 lower to 6.3 higher)
Drop out due to adverse events	135 (2 studies)	⊕⊕⊖⊖ LOW2,4 due to risk of bias, imprecision	Peto OR 2.73 (0.38 to 19.75)	15 per 1000	24 more per 1000 (from 9 fewer to 213 more)

1 Mean of final scores only, excluding change scores (Bilici 2010, Chung 2012, Langguth 2014)
2 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
3 Heterogeneity, I2=50%, p=0.04, unexplained by subgroup analysis.
4 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 4: Clinical evidence summary: rTMS (10 Hz) (high frequency) versus sham rTMS

Outcomes	No of	Quality of	Relati	Anticipated absolute effects

	Participants (studies) Follow up	the evidence (GRADE)	ve effect (95% CI)	Risk with Sham rTMS	Risk difference with rTMS (10 Hz) (high frequency) (95% CI)
Tinnitus severity (Tinnitus Handicap Inventory) Scale from: 0 to 100.	30 (1 study) Post-treatment	⨁⨁⨀⨀ LOW1 due to risk of bias		The mean tinnitus severity in the control groups was 0.7 change score	The mean tinnitus severity in the intervention groups was 10.4 lower (15.52 to 5.28 lower)
Tinnitus severity (Tinnitus Handicap Inventory) Scale from: 0 to 100.	30 (1 study) 6 months	⨁⨁⨀⨀ LOW1 due to risk of bias		The mean tinnitus severity in the control groups was 0.7 change score	The mean tinnitus severity in the intervention groups was 15.9 lower (22.34 to 9.46 lower)
Tinnitus severity (Tinnitus Severity Index) Scale from: 0 to 100.	30 (1 study) Post-treatment	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, imprecision		The mean tinnitus severity in the control groups was -0.6 change score	The mean tinnitus severity in the intervention groups was 1.5 lower (5.08 lower to 2.08 higher)
Tinnitus severity (Tinnitus Severity Index) Scale from: 0 to 100.	30 (1 study) 6 months	⨁⨁⨀⨀ LOW1 due to risk of bias		The mean tinnitus severity in the control groups was 1.1 change score	The mean tinnitus severity in the intervention groups was 7.8 lower (12.17 to 3.43 lower)
Anxiety (Beck Anxiety Inventory) Scale from: 0 to 63.	30 (1 study) Post-treatment	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, imprecision		The mean anxiety in the control groups was 13.0	The mean anxiety in the intervention groups was 2.3 higher (4.22 lower to 8.82 higher)
Anxiety (Beck Anxiety Inventory) Scale from: 0 to 63.	30 (1 study) 6 months	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, imprecision		The mean anxiety in the control groups was 14.1	The mean anxiety in the intervention groups was 0.9 higher (5.63 lower to 7.43 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Sham rTMS	Risk difference with rTMS (10 Hz) (high frequency) (95% CI)
at very high risk of bias 2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

Table 5: Clinical evidence summary: rTMS (1 Hz + 25 Hz) (combined frequency) versus sham rTMS

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Sham rTMS	Risk difference with RTMS (1 Hz + 25 Hz) (combined frequency) (95% CI)
Tinnitus severity (Tinnitus Handicap Inventory) Change score. Positive value indicates improvement.	31 (1 study) 1 months	⨁⨁⨀⨀ LOW1,2 due to risk of bias, imprecision		The mean tinnitus severity in the control groups was 0.2 change score	The mean tinnitus severity in the intervention groups was 4.3 higher (2.64 lower to 11.24 higher)
Tinnitus severity (Tinnitus Handicap Inventory) Change score. Positive value indicates improvement.	32 (1 study) 6 months	⨁⨁⨀⨀ LOW1,2 due to risk of bias, imprecision		The mean tinnitus severity in the control groups was 4.3 change score	The mean tinnitus severity in the intervention groups was 4.8 higher (2.64 lower to 12.24 higher)
Tinnitus severity (Tinnitus Handicap Questionnaire) Change score. Positive value indicates improvement.	31 (1 study) 1 months	⨁⨁⨀⨀ LOW1,2 due to risk of bias, imprecision		The mean tinnitus severity in the control groups was -1.1 change score	The mean tinnitus severity in the intervention groups was 2.6 higher (3.66 lower to 8.86 higher)
Tinnitus severity (Tinnitus Handicap Questionnaire) Change score. Positive value indicates improvement.	32 (1 study) 6 months	⨁⨁⨀⨀ LOW1,2 due to risk of bias, imprecision		The mean tinnitus severity in the control groups was 2.8 change score	The mean tinnitus severity in the intervention groups was 3.3 higher (3.27 lower to 9.87 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Sham rTMS	Risk difference with RTMS (1 Hz + 25 Hz) (combined frequency) (95% CI)
Depression (Beck Depression Inventory) Change score. Positive value indicates improvement.	31 (1 study) 1 months	⨁⨁⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean depression in the control groups was -0.6 change score	The mean depression in the intervention groups was 1.1 higher (2.03 lower to 4.23 higher)
Depression (Beck Depression Inventory Change score. Positive value indicates improvement.	32 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean depression in the control groups was 0 change score	The mean depression in the intervention groups was 0.1 higher (3.05 lower to 3.25 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 6: Clinical evidence summary: rTMS (27 MHz) (very high frequency) versus sham rTMS

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Sham rTMS	Risk difference with rTMS (27 MHz) (very high frequency) (95% CI)
Tinnitus severity (Tinnitus Handicap Inventory) Scale from: 0 to 100.	29 (1 study) 2 weeks	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean tinnitus severity in the control groups was 37.33	The mean tinnitus severity in the intervention groups was 7.9 lower (24.65 lower to 8.85 higher)
Tinnitus severity (Tinnitus Magnitude Rating, numeric rating scale)	35 (1 study)	⨁⊖⊖⊖ VERY		The mean tinnitus severity in the control groups was	The mean tinnitus severity in the intervention groups was

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Sham rTMS	Risk difference with rTMS (27 MHz) (very high frequency) (95% CI)
Scale from: 0 to 100.	2 weeks	LOW1,2 due to risk of bias, imprecision		58.67	9.38 lower (22.89 lower to 4.13 higher)
Patient-reported subjective worsening of tinnitus	37 (1 study) 2 weeks	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 0.84 (0.27 to 2.66)	263 per 1000	42 fewer per 1000 (from 192 fewer to 437 more)

1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
2 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias. Note: Difference in baseline outcome data – tinnitus severity (THI) - mean (SD): rTMS group 33.78 (22.15), sham group 39.30 (22.55); Tinnitus severity (Tinnitus Magnitude Rating) - mean (SD): rTMS group 51.11 (21.04), sham group 59.38 (17.5)

Table 7: Clinical evidence summary: Right dorsolateral prefrontal cortex (DLPFC) tDCS versus waiting-list control

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Waiting-list control	Risk difference with Right dorsolateral prefrontal cortex (DLPFC) tDCS (95% CI)
Tinnitus severity (Tinnitus Handicap Inventory) Scale from: 0 to 100.	42 (1 study) Post-treatment	⨁⨁⨁⊖ MODERATE 1 due to imprecision		The mean tinnitus severity in the control groups was 43.7	The mean tinnitus severity in the intervention groups was 3.1 lower (13.52 lower to 7.32 higher)
Tinnitus severity (Tinnitus Handicap Inventory) Scale from: 0 to 100.	42 (1 study) 3 months	⨁⨁⨁⊖ MODERATE 1		The mean tinnitus severity in the control groups was 45.0	The mean tinnitus severity in the intervention groups was 5.4 lower

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Waiting-list control	Risk difference with Right dorsolateral prefrontal cortex (DLPFC) tDCS (95% CI)
		due to imprecision			(18.05 lower to 7.25 higher)
Tinnitus severity (Subjective Tinnitus Severity Scale) Scale from: 0 to 16.	42 (1 study) Post-treatment	⨁⨁⨁⨀ MODERATE 1 due to imprecision		The mean tinnitus severity in the control groups was 10	The mean tinnitus severity in the intervention groups was 0.5 lower (1.94 lower to 0.94 higher)
Tinnitus severity (Subjective Tinnitus Severity Scale) Scale from: 0 to 16.	42 (1 study) 3 months	⨁⨁⨁⨀ MODERATE 1 due to imprecision		The mean tinnitus severity in the control groups was 10	The mean tinnitus severity in the intervention groups was 0.3 lower (1.87 lower to 1.27 higher)
Tinnitus severity (tinnitus intensity on VAS) Scale from: 0 to 100.	42 (1 study) Post-treatment	⨁⨁⨁⨀ MODERATE 1 due to imprecision		The mean tinnitus severity in the control groups was 41	The mean tinnitus severity in the intervention groups was 14.7 higher (-0.12 to 29.52 higher)
Tinnitus severity (tinnitus intensity on VAS) Scale from: 0 to 100.	42 (1 study) 3 months	⨁⨁⨀⨀ LOW1 due to imprecision		The mean tinnitus severity in the control groups was 53.1	The mean tinnitus severity in the intervention groups was 0.8 higher (12.18 lower to 13.78 higher)
Tinnitus severity (Clinical Global Impression Scale) Scale from: 0 to 7.	42 (1 study) Post-treatment	⨁⨁⨁⨀ MODERATE 1 due to imprecision		The mean tinnitus severity in the control groups was 4	The mean tinnitus severity in the intervention groups was 0 higher (0.34 lower to 0.34 higher)
Tinnitus severity (Clinical Global Impression Scale) Scale from: 0 to 7.	42 (1 study) 3 months	⨁⨁⨀⨀ LOW1 due to imprecision		The mean tinnitus severity in the control groups was 4	The mean tinnitus severity in the intervention groups was 0 higher (0.49 lower to 0.49 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Waiting-list control	Risk difference with Right dorsolateral prefrontal cortex (DLPFC) tDCS (95% CI)
Tinnitus distress (VAS) Scale from: 0 to 100.	42 (1 study) Post-treatment	⨁⨁⨁⊖ MODERATE 1 due to imprecision		The mean tinnitus distress in the control groups was 29.5	The mean tinnitus distress in the intervention groups was 11 higher (3.6 lower to 25.6 higher)
Tinnitus distress (VAS) Scale from: 0 to 100.	42 (1 study) 3 months	⨁⨁⨁⊖ MODERATE 1 due to imprecision		The mean tinnitus distress in the control groups was 49.2	The mean tinnitus distress in the intervention groups was 4.8 lower (18.91 lower to 9.31 higher)
Tinnitus annoyance (numeric rating scale) Scale from: 0 to 100.	13 (1 study) Post-treatment	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean tinnitus annoyance in the control groups was -11.54 change score	The mean tinnitus annoyance in the intervention groups was 16.1 higher (24.13 lower to 56.33 higher)
Tinnitus loudness (numeric rating scale 0-100) Scale from: 0 to 100.	13 (1 study) Post-treatment	⨁⨁⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean tinnitus loudness in the control groups was -2.44 change score	The mean tinnitus loudness in the intervention groups was 16.01 higher (13.94 lower to 45.96 higher)
Anxiety and depression (Hospital Anxiety and Depression Scale) Scale from: 0 to 21.	42 (1 study) 1 month	⨁⨁⨁⊖ MODERATE 1 due to imprecision		The mean anxiety and depression in the control groups was 15.3	The mean anxiety and depression in the intervention groups was 2.9 lower (7.2 lower to 1.4 higher)

1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
2 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 8: Clinical evidence summary: Left temporal area (LTA) tDCS versus sham tDCS

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Sham tDCS	Risk difference with Left temporal area (LTA) tDCS (95% CI)
Tinnitus severity (Tinnitus Handicap Inventory) Scale from: 0 to 100.	20 (1 study) Post-treatment	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean tinnitus severity in the control groups was 54.1	The mean tinnitus severity in the intervention groups was 4.5 higher (18.77 lower to 27.77 higher)
Tinnitus severity (Tinnitus Handicap Inventory) Scale from: 0 to 100.	20 (1 study) 2 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean tinnitus severity in the control groups was 53.4	The mean tinnitus severity in the intervention groups was 2.4 higher (21.55 lower to 26.35 higher)
Tinnitus distress Scale from: 0 to 10.	20 (1 study) Post-treatment	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean tinnitus distress in the control groups was 4.5	The mean tinnitus distress in the intervention groups was 0.5 higher (1.26 lower to 2.26 higher)
Tinnitus distress Scale from: 0 to 10.	20 (1 study) 2 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean tinnitus distress in the control groups was 4.2	The mean tinnitus distress in the intervention groups was 0.8 higher (1.22 lower to 2.82 higher)
Tinnitus loudness Scale from: 0 to 10.	20 (1 study) Post-treatment	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias,		The mean tinnitus loudness in the control groups was 5	The mean tinnitus loudness in the intervention groups was 0.2 lower (2.22 lower to 1.82 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Sham tDCS	Risk difference with Left temporal area (LTA) tDCS (95% CI)
		imprecision			
Tinnitus loudness Scale from: 0 to 10.	20 (1 study) 2 weeks	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, imprecision		The mean tinnitus loudness in the control groups was 4.8	The mean tinnitus loudness in the intervention groups was 0.3 higher (2.03 lower to 2.63 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 9: Clinical evidence summary: VNS versus sham VNS

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Sham VNS	Risk difference with Vagal Nerve Stimulation (VNS) (95% CI)
Tinnitus severity (Tinnitus Handicap Inventory) Scale from: 0 to 100.	30 (1 study) Post-treatment	⨁⨁⨁⨀ MODERATE1 due to imprecision		The mean tinnitus severity in the control groups was -7.3	The mean tinnitus severity in the intervention groups was 10.4 lower (32.26 lower to 11.46 higher)
Tinnitus severity (Tinnitus Handicap Questionnaire) Scale from: 0 to 100.	30 (1 study) Post-treatment	⨁⨁⨁⨀ MODERATE1 due to imprecision		The mean tinnitus severity in the control groups was -7.5 change score	The mean tinnitus severity in the intervention groups was 5 higher (4.66 lower to 14.66 higher)
Tinnitus severity (Tinnitus Functional Index)	30	⨁⨁⨁⨀		The mean tinnitus severity in the control groups was	The mean tinnitus severity in the intervention groups was

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Sham VNS	Risk difference with Vagal Nerve Stimulation (VNS) (95% CI)
Scale from: 0 to 100.	(1 study) Post-treatment	MODERATE1 due to imprecision		-7.5	5.47 higher (3.87 lower to 14.81 higher)
Tinnitus loudness Scale from: 0 to 100.	30 (1 study) Post-treatment	⨁⨁⊖⊖ LOW1 due to imprecision		The mean tinnitus loudness (post-treatment) in the control groups was -8.5	The mean tinnitus loudness in the intervention groups was 1.81 higher (13.22 lower to 16.84 higher)
1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

Table 10: Clinical evidence summary: Acoustic CR versus placebo/sham

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo/sham	Risk difference with Acoustic CR neuromodulation (95% CI)
Tinnitus severity (Tinnitus Questionnaire) Scale from: 0 to 100.	63 (1 study) Post-treatment	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean tinnitus severity in the control groups was -8.4 change score	The mean tinnitus severity in the intervention groups was 2.37 lower (9.17 lower to 4.43 higher)
Tinnitus severity (Tinnitus Questionnaire) Scale from: 0 to 100.	63 (1 study) 4 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness,		The mean tinnitus severity in the control groups was -9.2 change score	The mean tinnitus severity in the intervention groups was 2.58 lower (12.34 lower to 7.18 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo/sham	Risk difference with Acoustic CR neuromodulation (95% CI)
		imprecision			
Tinnitus annoyance Scale from: 0 to 100.	63 (1 study) Post-treatment	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean tinnitus annoyance in the control groups was -2.0 change score	The mean tinnitus annoyance in the intervention groups was 13.21 lower (28.75 lower to 2.33 higher)
Tinnitus annoyance Scale from: 0 to 100.	63 (1 study) 4 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean tinnitus annoyance in the control groups was 2.0 change score	The mean tinnitus annoyance in the intervention groups was 12.61 lower (42.62 lower to 17.4 higher)
Tinnitus loudness Scale from: 0 to 100.	63 (1 study) Post-treatment	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean tinnitus loudness in the control groups was -9.0 change score	The mean tinnitus loudness in the intervention groups was 3.01 lower (20.41 lower to 14.39 higher)
Tinnitus loudness Scale from: 0 to 100.	63 (1 study) 4 weeks	⨁⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, indirectness, imprecision		The mean tinnitus loudness in the control groups was -1.0 change score	The mean tinnitus loudness in the intervention groups was 10.19 lower (36.13 lower to 15.75 higher)

1 The majority of the evidence is pooled from one study in which four different treatment types/protocols (featuring different frequencies of intervention and

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo/sham	Risk difference with Acoustic CR neuromodulation (95% CI)
different intervention lengths) were used 2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs 3 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias. Note: Significant outcome differences at baseline, Tinnitus Questionnaire score 0-100 (mean): Acoustic CR group 42.25, sham group 29.2; Significant outcome differences at baseline, tinnitus annoyance score 0-100 (mean): Acoustic CR group 63.9, sham group 38.0; Significant outcome differences at baseline, tinnitus loudness score 0-100 (mean): Acoustic CR group 65.35, sham group 43.0					

See appendix F for full GRADE tables.

1.5 Economic evidence

1.5.1 Included studies

No relevant health economic studies were identified.

1.5.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in appendix G.

1.5.3 Unit costs

Table 11: UK cost of magnetic stimulator

Stimulator [a]	Cost	Annuitized cost per patient [b]
MagPro R-30 [c]	£42,000	£18.92
SuperRapid [c]	£27,850	£12.55
Coils	£1800 – £2000	£1.23 - £1.37
10 sessions of 30 minute duration with band 7 audiologist (300 minutes) [d]	£265	
Total Cost MagPro R-30	£42,265	£285.15 - £285.29
Total cost SuperRapid	£28,115	£278.78 - £278.92

(a) Prices for rTMS stimulators are not readily available. Discussions took place with the manufacturers to establish a guide price.

(b) Device costs were annuitized to calculate annual equivalent costs device. The formula used to calculate annuitized annual costs is as follows:
$E = K – [S / (1+r)n] / A(n,r)$
Where E = equivalent annual cost; K = Purchase price of the oximetry device; S = resale value; r = discount (interest) rate; n = equipment lifespan; A(n,r) = annuity factor (n years at interest rate r). The following assumptions were used: resale value of £0, discount rate of 3.5% and equipment lifespan of 8 years for the rTMS device and 5 years for the coils.

(c) It was assumed that the MagPro R-30 and SuperRapid would have a lifespan of 8 years. If it is assumed that the device can be used Monday to Friday from 9am to 6pm, then per annum the device can be used on 312 patients. The costs have been adjusted accordingly to reflect the costs incurred by per patient (5 hours) for using the programming station.

(d) Number of sessions estimated from studies included in the clinical review. Session length estimated from GC.

Table 12: UK cost of Acoustic Neuromodulation

Stimulator [a]	Cost	Annuitized costs per patient [b]
Acoustic CR Neuromodulation Device including medical earphones	£1,850	£478.50 [c]
Rechargeable Batteries	£20	£7.63 [c]
Programming Station	£1500	£0.72 [d]
1 fitting appointment and 5 recalibration appointment with Band 7 audiologist (210 minutes)	£185.50	£185.50
Total Costs	£3555.50	£672.35

(a) Costs and assumptions have been derived from NICE's medtech innovation briefing on acoustic CR neuromodulation for adults with chronic subjective tonal tinnitus.

(b) Device costs were annuitized to calculate annual equivalent costs device. The formula used to calculate annuitized annual costs is as follows:

E = K – [S / (1+r)n] / A(n,r)
Where E = equivalent annual cost; K = Purchase price of the oximetry device; S = resale value; r = discount (interest) rate; n = equipment lifespan; A(n,r) = annuity factor (n years at interest rate r). The following assumptions were used: resale value of £0, discount rate of 3.5% and equipment lifespan of 3 years for neuromodulation device, 5 years for programming station and 2 years for rechargeable batteries.

(c) It was assumed that the treatment duration would be 9 months and then the device would be returned for re-use by another patient. The annuitized costs have been adjusted to reflect the costs over the treatment duration.

(d) It was assumed that the programming station would be required during the fitting and recalibration appointments. If it is assumed that the device can be used Monday to Friday from 9am to 6pm, then per annum the device can be used on 446 patients. The costs have been adjusted accordingly to reflect the costs incurred by per patient (3.5 hours) for using the programming station.

1.6 Evidence statements

1.6.1 Clinical evidence statements

- **1 Hz rTMS versus sham rTMS**

Nine studies (n=589) were included in this comparison. Clinical evidence was reported for all critical outcomes. There was no clinical difference between 1 Hz rTMS and sham rTMS for tinnitus severity on most scales, apart from tinnitus severity on tinnitus functional index (TFI) at 6 months follow –up and tinnitus severity on VAS at post-treatment and 3 month follow-up, for which there was clinical benefit of 1 Hz rTMS.

There was clinical benefit of 1 Hz rTMS for tinnitus distress (on VAS) and tinnitus annoyance (on VAS) at both post-treatment and 3 months follow-up. There was a clinical benefit of sham rTMS for drop out due to adverse event only. For all other outcomes in comparison there was no clinical difference between 1 Hz rTMS and sham.

- **10 Hz rTMS versus sham rTMS**

One study (n=30) was included in this comparison. No clinical evidence was reported for the critical outcomes of tinnitus annoyance, tinnitus loudness and quality of life. There was clinical benefit of 10 Hz rTMS for tinnitus severity on the tinnitus handicap inventory (THI) at both post-treatment and 6 months follow-up. There was no clinical difference between 10 Hz rTMS and sham rTMS for tinnitus severity on the tinnitus severity index (TSI) and anxiety on the Beck Anxiety Inventory).

- **Combined 1 Hz + 25 Hz rTMS versus sham rTMS**

One study (n=32) was included in this comparison. No clinical evidence was reported for the critical outcomes of tinnitus annoyance, tinnitus loudness and quality of life. There was no clinical difference between combined frequency rTMS and sham rTMS for the outcomes reported (tinnitus severity on the THI and the Tinnitus Handicap Questionnaire) and depression on the Beck Depression Inventory).

- **27 MHz rTMS versus sham rTMS**

One study (n=37) was included in this comparison. No clinical evidence was found for the critical outcomes of tinnitus annoyance, tinnitus loudness and quality of life. There was no clinical difference between 27 MHz rTMS and sham rTMS for the outcomes reported (tinnitus severity on the THI and Tinnitus Magnitude Rating scale and patient-reported worsening if tinnitus).

- **tDCS (right dorsolateral prefrontal cortex, DLPFC) versus sham tDCS**

Two studies (n=55) were included in this comparison. No clinical evidence was found for the critical outcome of quality of life. There was clinical harm of tDCS (DLPFC) for tinnitus

severity (on VAS), tinnitus distress (on VAS), tinnitus loudness (on VAS/NRS) and tinnitus loudness (on VAS/NRS) all at post-treatment. There was no clinical difference between tDCS (DLPFC) and sham rDCS for all other outcomes (tinnitus severity on THI, Subjective Tinnitus Severity Scale, Clinical Global Impression Scale for both time points, tinnitus severity on VAS at 3 month follow-up, tinnitus distress on VAS at 3 month follow-up, and anxiety and depression on the Hospital Anxiety and Depression Scale at 1 month follow-up).

- **tDCS (left temporal area, LTA) versus sham tDCS**

One study (n=20) was included in this comparison. No clinical evidence was found for the critical outcomes of tinnitus annoyance and quality of life. There was no clinical difference between tDCS (LTA) and sham tDCS for all reported outcomes (tinnitus severity on THI, tinnitus distress on VAS and tinnitus loudness on VAS at post-treatment and 2 weeks follow-up.

- **VNS versus sham VNS**

One study (n=30) was included in this comparison. No clinical evidence was found for the critical outcomes of tinnitus annoyance and quality of life. There was clinical benefit of VNS for tinnitus severity (on the THI). There was no clinical difference between VNS and sham for all other reported outcomes (tinnitus severity on the Tinnitus Handicap Questionnaire, tinnitus severity on the TFI and tinnitus loudness on VAS, all at post-treatment only.

- **Acoustic CR versus sham acoustic CR**

One study (n=63) was included in this comparison. No clinical evidence was found for the critical outcome of quality of life. There was a clinical benefit of acoustic CR for tinnitus annoyance (on VAS) at both post-treatment and 4 week follow-up time points, and for tinnitus loudness (on VAS) at 4 weeks follow-up. There was no clinical difference between acoustic CR and sham for all other outcomes reported (tinnitus severity on the Tinnitus Questionnaire post-treatment and at 4 weeks follow-up and tinnitus loudness (on VAS) at 4 weeks follow-up.

1.6.2 Health economic evidence statements

- No relevant economic evaluations were identified.

1.7 The committee's discussion of the evidence

1.7.1 Interpreting the evidence

1.7.1.1 The outcomes that matter most

Tinnitus distress, annoyance and tinnitus severity were critical outcomes as they were thought to be common factors for people with tinnitus and impact their quality of life. Quality of life (tinnitus-related) and general quality of life were also critical outcomes due to their impact on the person with tinnitus.

Tinnitus loudness, anxiety, depression, sleep, safety, tolerability (drop-outs/adherence) and side effects were thought to be important outcomes.

1.7.1.2 The quality of the evidence

1 Hz rTMS versus sham rTMS

Nine studies were identified for this comparison, with evidence across the following 13 outcomes: tinnitus severity (divided into five outcomes based on the Tinnitus Handicap Inventory, Tinnitus Questionnaire, Tinnitus Severity Index, Tinnitus Functional Index and

Visual Analogue Scale), health-related quality of life (on the SF-12 physical and mental components, separately), tinnitus distress on VAS, tinnitus annoyance on VAS, anxiety (Beck Anxiety Inventory), depression (Beck Depression Inventory), tinnitus loudness on VAS and dropout due to adverse events. Each outcome had data at two points: post-treatment and at follow-up (between 1 and 6 months), with the exception of tinnitus loudness (1 month only) and drop out due to adverse events.

The majority of evidence in this comparison was of very low or low quality (19), with a small number of outcomes of moderate to high quality (5). Downgrading of the evidence was mostly due to risk of bias and imprecision.

10 Hz rTMS versus sham rTMS

Evidence for this comparison came from one study only (n=30), comparing 10 Hz rTMS against sham rTMS for tinnitus severity (on the Tinnitus Handicap Inventory and Tinnitus Severity Index) and anxiety (on the Beck Anxiety Index), each at post-treatment and 6 month follow-up time points. All evidence for this comparison was of very low or low quality due to risk of bias and imprecision.

Combined 1 Hz + 25 Hz rTMS versus sham rTMS

Evidence for this comparison came from a single study (n=32), comparing 1 Hz and 25 Hz combined rTMS against sham rTMS for tinnitus severity (on the Tinnitus Handicap Inventory and Tinnitus Handicap Questionnaire) and depression (on the Beck Depression Inventory), all at post-treatment and 6 months follow-up time points. Evidence in this comparison ranged from low to very low (downgraded due to risk of bias and imprecision).

27 MHz rTMS versus sham rTMS

Evidence for this comparison came from a single study (n=37), comparing 27.12 MHz rTMS against sham rTMS for tinnitus severity (on the Tinnitus Handicap Inventory and Tinnitus Magnitude Rating (a numeric rating scale)) and worsening of tinnitus, both at post-treatment. The evidence for the three outcomes in this comparison was of very low quality, downgraded due to risk of bias (including significant difference in outcome at baseline) and imprecision.

tDCS (right dorsolateral prefrontal cortex, DLPFC) versus sham tDCS

Evidence for this comparison came from two studies (n=55) across eight outcomes: tinnitus severity (on Tinnitus Handicap Inventory, Subjective Tinnitus Severity Scale, VAS and Clinical Global Impression Scale, each included here as separate outcomes) and tinnitus distress (VAS) at post-treatment and 3 month follow-up time points; tinnitus loudness and tinnitus annoyance (VAS) at post-treatment; and anxiety and depression (Hospital Anxiety and Depression Scale) at 1 month follow-up.

Most of the evidence in this comparison was of moderate quality (downgraded for imprecision) with the rest of low or very low quality (4 outcome time points) due to risk of bias as well as imprecision.

tDCS (left temporal area, LTA) versus sham tDCS

Evidence for this comparison came from a single study (n=20) reporting three outcomes: tinnitus severity (Tinnitus Handicap Inventory), tinnitus distress (VAS) and tinnitus loudness (VAS), each at post-treatment and 2 weeks follow-up time points. All of this evidence was of low quality due to risk of bias and imprecision.

VNS versus sham VNS

Evidence for this comparison came from a single study (n=30) reporting four outcomes: tinnitus severity (on Tinnitus Handicap Inventory and Tinnitus Questionnaire), tinnitus severity (VAS) and tinnitus loudness (VAS), all at post-treatment. Three of these outcomes

had evidence of moderate quality, with one outcome (tinnitus loudness) of low quality. All downgrading of the evidence was due to imprecision.

Acoustic CR versus sham acoustic CR

Evidence for this comparison came from a single study (n=63) with three outcomes: tinnitus severity (Tinnitus Questionnaire), tinnitus annoyance (VAS) and tinnitus loudness (VAS), each at post-treatment and 4 week follow-up time points. All of the evidence in this comparison was of very low quality due to risk of bias, imprecision and indirectness. It should be noted that risk of bias was due to a large difference in the intervention and control groups at baseline for each of the outcomes. Indirectness was due to the intervention group being a pooling of 4 different intervention groups, each receiving a different frequency/pattern of acoustic CR neuromodulation (total pooled intervention group n=58; control n=5).

1.7.1.3 Benefits and harms

For low-frequency (1 Hz) rTMS, all evidence in this comparison showed no clinically important difference between the intervention and sham control. The only outcomes that showed benefit of 1 Hz rTMS were tinnitus severity (VAS) at post-treatment and 3 month follow-up, both taken from the same single study (n=39), and tinnitus severity (Tinnitus Functional Index) at 6 months, which was also taken from a single study (n=64). There were fewer dropouts due to adverse events in the sham group (64 less per 1000) based on two studies (n=135). The small volume of evidence mostly showing a lack of clinically important difference between active rTMS (1 Hz) and sham rTMS, is reflected in the committee's decision not to make a recommendation.

For all other comparisons there was generally not enough evidence to conclude benefit or harm of the intervention. Most outcomes under each comparison showed no clinically important difference between active treatment and sham treatment, with all outcomes based only on single studies with relatively small participant numbers. The committee acknowledged this and decided that they would make a research recommendation to promote the need for expansion of this evidence base around neuromodulation for tinnitus.

Overall, the committee decided not make a recommendation due to the very limited evidence of benefit or harm for any of the interventions in this review. In areas with the most evidence (rTMS), most outcomes showed no clinically important difference between intervention and control. While the committee were able to make recommendations for other reviews based on very limited evidence, they decided that because neuromodulation interventions are currently not offered for tinnitus on the NHS, any recommendation would have a large impact on current practice and there was therefore not enough evidence to support this change.

Due to the limited amount of evidence found in this review the committee decided to make a research recommendation to encourage further trials of neuromodulation interventions for tinnitus. While there were often a very small number of dropouts due to negative effects in the trials reviewed here, the committee added the caveat that the long-term safety of rTMS and other neuromodulation interventions is unknown, particularly in children and young people, and should be taken into consideration before carrying out any research in this area.

1.7.2 Cost effectiveness and resource use

There were no economic evaluations available for this question. The committee were of the view that the use of neuromodulation was not justified in the absence of clear clinical effectiveness data. This view was reinforced when the committee were presented with the high unit costs for some of these interventions. The committee agreed that more research was required which used quality of life (using the EQ-5D) as an outcome measure so that cost-effectiveness of the intervention could be established in the future.

1.7.3 Other factors the committee took into account

Questions were raised about what evidence there is for long-term safety of neuromodulation interventions such as rTMS and tDCS. Committee members suggested that the long-term impact of these techniques is unknown (and not covered by the evidence in this review) and this should be taken into consideration when planning future research and making recommendations.

Of particular concern was the safety of these neuromodulation interventions in children. This is reflected in the committee's research recommendations, which only refer to adults. It was concluded that there should be evidence of the safety of these techniques for use in children and young people before conducting extensive research of efficacy.

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Appendices

Appendix A: Review protocols

Table 13: Review protocol: Neuromodulation for tinnitus

ID	Field	Content
0.	PROSPERO registration number	Not registered
1.	Review title	The clinical and cost effectiveness of neuromodulation for people with tinnitus
2.	Review question	What is the clinical and cost effectiveness of neuromodulation for people with tinnitus?
3.	Objective	The review aims to evaluate the clinical effectiveness and cost-effectiveness of different forms of neuromodulation that are utilised by different healthcare professionals for the management of tinnitus.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • CINAHL, Current Nursing and Allied Health Literature Searches will be restricted by: • English language • Human studies • Letters and comments are excluded. Other searches: • Inclusion lists of relevant systematic

		reviews will be checked by the reviewer. The searches may be re-run 6 weeks before final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Tinnitus
6.	Population	Inclusion: Children, young people and adults with tinnitus and hearing loss Strata: • Children/young people (up to 18 years) • Adults Exclusion: None
7.	Intervention/Exposure/Test	• transcranial direct current stimulation (tDCS) • transcranial alternating current stimulation (tACS) • vagal nerve stimulation (VNS) • transcutaneous vagal nerve stimulation (tVNS) • acoustic neuromodulation therapy • paired electrical and acoustic stimulation therapy • repetitive transcranial magnetic stimulation (rTMS)
8.	Comparator/Reference standard/Confounding factors	• Interventions compared with each other • Control group (no intervention, sham intervention or waiting-list control) • Sound therapy and sound enrichment o sound enrichment (e.g. environmental sound, a CD or mp3 download or the radio, a smartphone App, bedside/table-top sound generators, a wearable sound generator) o Customised sound-based therapies, e.g. amplitude modulated tones and notched noise/music o Masking

		• Amplification devices for people with hearing loss o Hearing aids o Implantable devices (including cochlear implants, bone-anchored hearing aids, bone-conduction hearing implants, bone-bridge/middle-ear devices) • Combination device (sound generator and hearing aids) • Tinnitus education including coping strategies, provision of information and advice and relaxation
9.	Types of study to be included	• Systematic reviews • RCTs • If there is an inadequate amount of RCT data, non-randomised comparative studies will be considered
10.	Other exclusion criteria	• Non-English language studies • Studies will only be included if they report one or more of the outcomes listed above. • Descriptive (non-comparative) studies will be excluded
11.	Context	N/A
12.	Primary outcomes (critical outcomes)	• Tinnitus severity Impact of tinnitus: • Tinnitus distress • Tinnitus annoyance Health related QoL: • QoL (tinnitus) • QoL
13.	Secondary outcomes (important outcomes)	Tinnitus percept: • Tinnitus loudness Other co-occurring complaints: • Depression • Anxiety • Anxiety and depression • Sleep

		Adverse events: • Safety • Tolerability/adherence/drop-outs/attrition • Side effects (e.g. worsening of tinnitus)
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened for inclusion. The full text of potentially eligible studies will be retrieved and will be assessed for eligibility in line with the criteria outlined above. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. An in-house developed database; EviBase, will be used for data extraction. A standardised form is followed to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and for undertaking assessment of study quality. Summary evidence tables will be produced including information on: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings. A second reviewer will quality-assure the extracted data. Discrepancies will be identified and resolved through discussion (with a third reviewer where necessary).
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews the following checklist will be used according to study design being assessed: • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS)

		• Randomised Controlled Trial: Cochrane RoB (2.0) Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and 95% confidence intervals will be calculated for each outcome. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects. GRADE pro will be used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. Other bias will only be taken into consideration in the quality assessment if it is apparent. Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. If sufficient data is available to make a network of treatments, WinBUGS will be used for network meta-analysis.
17.	Analysis of sub-groups	• Profoundly deaf

		• People with learning disability or cognitive impairment • Mild hearing loss		
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	29/05/18		
22.	Anticipated completion date	11/03/20		
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☐	☑
		Piloting of the study selection process	☐	☑
		Formal screening of search results against eligibility criteria	☐	☑
		Data extraction	☐	☑
		Risk of bias (quality)	☐	☑

		assessment		
		Data analysis	☐	☑
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail Tinnitus@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre: • Dr Jennifer Hill [Guideline lead] • Ms Sedina Lewis/Ms Julie Neilson [Senior systematic reviewers] • Dr Richard Clubbe [Systematic reviewer] • Mr David Wonderling [Health economist lead] • Mr Emtiyaz Chowdhury [Health economist] • Ms Jill Cobb [Information specialist] • Dr Giulia Zuodar [Project manager]		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		

28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].
29.	Other registration details	N/A
30.	Reference/URL for published protocol	N/A
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Tinnitus, neuromodulation
33.	Details of existing review of same topic by same authors	N/A
34.	Current review status	☐ Ongoing ☒ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	N/A
36.	Details of final publication	www.nice.org.uk

Table 14: Health economic review protocol

Review	All questions – health economic evidence

question	
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2003, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[34] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

	Health economic study type: • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2003 or later but that depend on unit costs and resource data entirely or predominantly from before 2003 will be rated as 'Not applicable'. • Studies published before 2003 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[34]

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 4: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 02 April 2019	Exclusions
Embase (OVID)	1974 – 02 April 2019	Exclusions
The Cochrane Library (Wiley)	Cochrane Reviews to 2019 Issue 4 of 12 CENTRAL to 2019 Issue 4 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 4 of 4	None
CINAHL, Current Nursing and Allied Health Literature (EBSCO)	Inception – 02 April 2019	Exclusions

Medline (Ovid) search terms

1.	Tinnitus/
2.	tinnit*.ti,ab.
3.	1 or 2
4.	letter/
5.	editorial/
6.	news/
7.	exp historical article/
8.	Anecdotes as Topic/
9.	comment/
10.	case report/
11.	(letter or comment*).ti.
12.	or/4-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animals/ not humans/
16.	exp Animals, Laboratory/
17.	exp Animal Experimentation/
18.	exp Models, Animal/

19.	exp Rodentia/
20.	(rat or rats or mouse or mice).ti.
21.	or/14-20
22.	3 not 21
23.	limit 22 to English language

Embase (Ovid) search terms

1.	tinnitus/
2.	tinnit*.ti,ab.
3.	1 or 2
4.	letter.pt. or letter/
5.	note.pt.
6.	editorial.pt.
7.	Case report/ or Case study/
8.	(letter or comment*).ti.
9.	or/4-8
10.	randomized controlled trial/ or random*.ti,ab.
11.	9 not 10
12.	animal/ not human/
13.	Nonhuman/
14.	exp Animal Experiment/
15.	exp Experimental animal/
16.	Animal model/
17.	exp Rodent/
18.	(rat or rats or mouse or mice).ti.
19.	or/11-18
20.	3 not 19
21.	limit 20 to English language

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Tinnitus] explode all trees
#2.	tinnit*:ti,ab
#3.	#1 or #2

CINAHL (EBSCO) search terms

S1.	(MH "Tinnitus")
S2.	(MH "Tinnitus Retraining Therapy")
S3.	tinnit*
S4.	S1 OR S2 OR S3
S5.	PT anecdote or PT audiovisual or PT bibliography or PT biography or PT book or PT book review or PT brief item or PT cartoon or PT commentary or PT computer program or PT editorial or PT games or PT glossary or PT historical material or PT interview or PT letter or PT listservs or PT masters thesis or PT obituary or PT pamphlet or PT pamphlet chapter or PT pictorial or PT poetry or PT proceedings or PT “questions and answers” or PT response or PT software or PT teaching materials or PT website
S6.	S4 NOT S5

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to the tinnitus population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics and quality of life studies

Table 5: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2002 – 02 March 2019	Exclusions Health economics studies Quality of life studies
Embase	2002 – 02 March 2019	Exclusions Health economics studies Quality of life studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 31 Mar 2018 NHSEED - Inception to March 2015	None

Medline (Ovid) search terms

1.	Tinnitus/
2.	tinnit*.ti,ab.
3.	1 or 2
4.	letter/
5.	editorial/
6.	news/
7.	exp historical article/
8.	Anecdotes as Topic/
9.	comment/
10.	case report/
11.	(letter or comment*).ti.
12.	or/4-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animals/ not humans/
16.	exp Animals, Laboratory/
17.	exp Animal Experimentation/
18.	exp Models, Animal/
19.	exp Rodentia/
20.	(rat or rats or mouse or mice).ti.
21.	or/14-20
22.	3 not 21
23.	limit 22 to English language
24.	Economics/
25.	Value of life/

26.	exp "Costs and Cost Analysis"/
27.	exp Economics, Hospital/
28.	exp Economics, Medical/
29.	Economics, Nursing/
30.	Economics, Pharmaceutical/
31.	exp "Fees and Charges"/
32.	exp Budgets/
33.	budget*.ti,ab.
34.	cost*.ti.
35.	(economic* or pharmaco?economic*).ti.
36.	(price* or pricing*).ti,ab.
37.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
38.	(financ* or fee or fees).ti,ab.
39.	(value adj2 (money or monetary)).ti,ab.
40.	or/24-39
41.	quality-adjusted life years/
42.	sickness impact profile/
43.	(quality adj2 (wellbeing or well being)).ti,ab.
44.	sickness impact profile.ti,ab.
45.	disability adjusted life.ti,ab.
46.	(qal* or qtime* or qwb* or daly*).ti,ab.
47.	(euroqol* or eq5d* or eq 5*).ti,ab.
48.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
49.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
50.	(hui or hui1 or hui2 or hui3).ti,ab.
51.	(health* year* equivalent* or hye or hyes).ti,ab.
52.	discrete choice*.ti,ab.
53.	rosser.ti,ab.
54.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
55.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
56.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
57.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
58.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
59.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
60.	or/41-59
61.	23 and (40 or 60)

Embase (Ovid) search terms

1.	tinnitus/
2.	tinnit*.ti,ab.
3.	1 or 2
4.	letter.pt. or letter/
5.	note.pt.
6.	editorial.pt.

7.	Case report/ or Case study/
8.	(letter or comment*).ti.
9.	or/4-8
10.	randomized controlled trial/ or random*.ti,ab.
11.	9 not 10
12.	animal/ not human/
13.	Nonhuman/
14.	exp Animal Experiment/
15.	exp Experimental animal/
16.	Animal model/
17.	exp Rodent/
18.	(rat or rats or mouse or mice).ti.
19.	or/11-18
20.	3 not 19
21.	health economics/
22.	exp economic evaluation/
23.	exp health care cost/
24.	exp fee/
25.	budget/
26.	funding/
27.	budget*.ti,ab.
28.	cost*.ti.
29.	(economic* or pharmaco?economic*).ti.
30.	(price* or pricing*).ti,ab.
31.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
32.	(financ* or fee or fees).ti,ab.
33.	(value adj2 (money or monetary)).ti,ab.
34.	or/21-33
35.	quality adjusted life year/
36.	"quality of life index"/
37.	short form 12/ or short form 20/ or short form 36/ or short form 8/
38.	sickness impact profile/
39.	(quality adj2 (wellbeing or well being)).ti,ab.
40.	sickness impact profile.ti,ab.
41.	disability adjusted life.ti,ab.
42.	(qal* or qtime* or qwb* or daly*).ti,ab.
43.	(euroqol* or eq5d* or eq 5*).ti,ab.
44.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
45.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
46.	(hui or hui1 or hui2 or hui3).ti,ab.

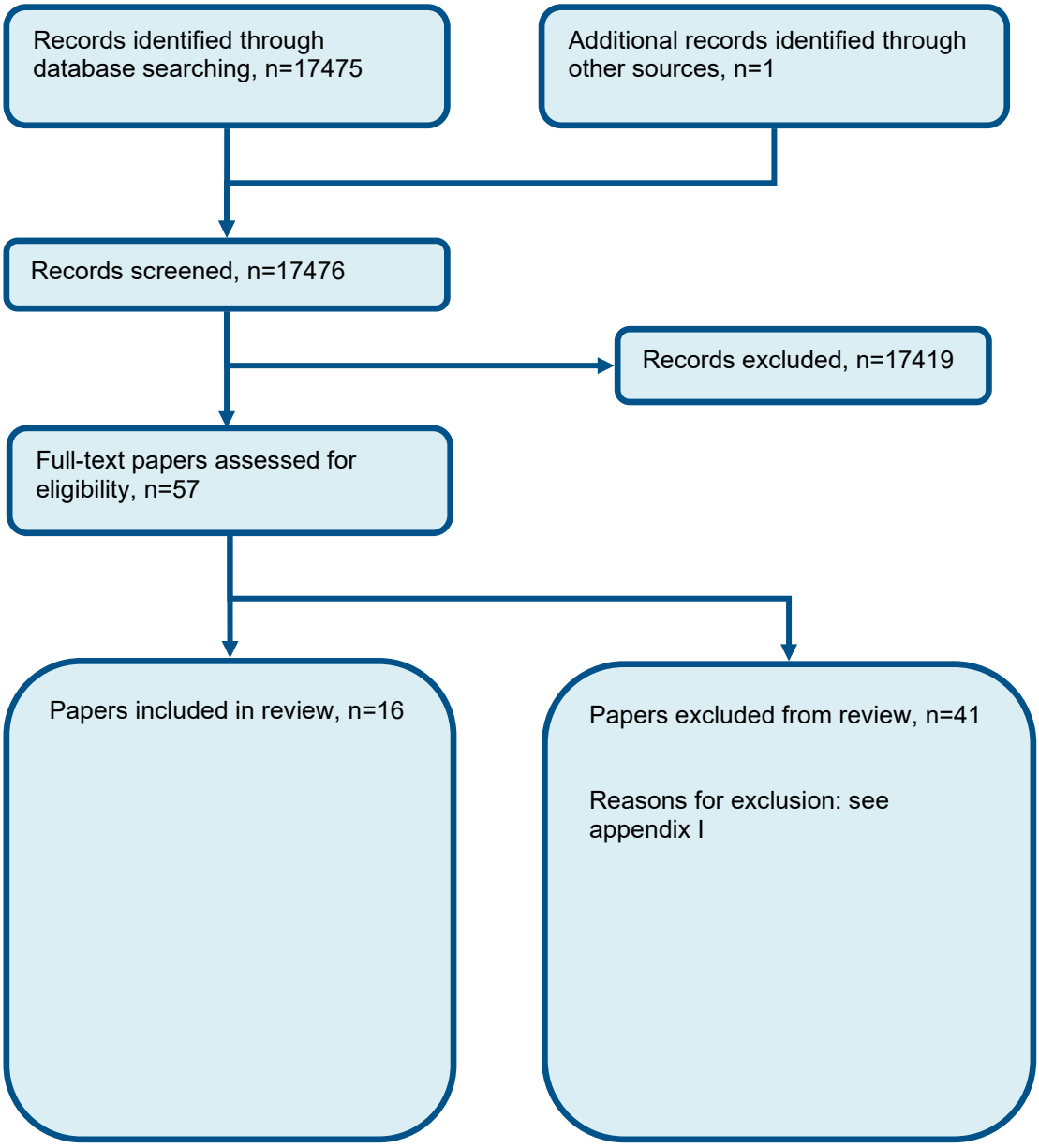
47.	(health* year* equivalent* or hye or hyes).ti,ab.
48.	discrete choice*.ti,ab.
49.	rosser.ti,ab.
50.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
51.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
52.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
53.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
54.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
55.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
56.	or/35-55
57.	20 and (34 or 56)
58.	limit 57 to English language

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Tinnitus EXPLODE ALL TREES
#2.	(tinnit*)
#3.	#1 OR #2

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of neuromodulation for the management of tinnitus



Appendix D: Clinical evidence tables

Study	Anders 2010[2]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=52)
Countries and setting	Conducted in Czech Republic
Line of therapy	Unclear
Duration of study	Intervention + follow up: 2 weeks + 26 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Unilateral or bilateral tinnitus according to the International Classification of Diseases (ICD-10) 10th Revision (H 93.1)
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Right handedness, female and male subjects aged 18 to 70 years naive with regards to rTMS, written informed consent, unilateral or bilateral tinnitus according to the International Classification of Diseases (ICD-10) 10th Revision (H 93.1) of at least 6 months duration, pharmacological treatment for at least 3 months without significant clinical response, identical doses of current pharmacological treatment for at least 6 weeks, age-adjusted normal sensorineural hearing determined by audiogram within the last 6 weeks before start of study, i.e. no more than 5 dB below the 10% percentile (DIN EN ISO 7029) of the appropriate age and gender group in all measured standard frequencies, a normal neurological exam and normal cranial magnetic resonance imaging finding. Normal middle ear status was demonstrated by tympanometry, stapedius reflex tests and otoscopy.
Exclusion criteria	Concurrent other forms of tinnitus treatments, a history of neuropsychiatric disorder (personal or family history of epilepsy, documented abnormal EEG, intracranial hypertension, a history of dizziness, significant head injury, stroke, aneurysm, brain malformation, neurodegenerative disorder affecting the brain, previous cranial

	neurosurgery, presence of acoustic neuroma, glomus tumor, brain tumor, profound hearing loss >90 dB threshold and 4 000 Hz or active Meniere disease), pacemaker and other metal implants, implanted medication pump, pregnancy, lactation, presence of other significant medical condition (neuroendocrine, cardiovascular, cerebrovascular, systemic autoimmune diseases), concomitant psychotropic medication or medication that lowers seizure threshold (tricyclic antidepressants or bupropion) or reduces cortical excitation (anticonvulsants, benzodiazepines or other sedatives). Concomitant axis I psychiatric disorders according to ICD-10. Patients unable to fulfil; the study requirements and those unable to communicate reliably with the investigators or those unlikely to cope with the trial requirements. Participation in a clinical trial within the last 30 days.
Recruitment/selection of patients	Study participants were recruited amongst outpatients seeking treatment at the Department of Otorhinolaryngology, Head and Neck Surgery of the First Faculty of Medicine and Motol Teaching Hospital, Charles University, Prague.
Age, gender and ethnicity	Age - Mean (SD): rTMS group 48.09 (12.86) ; sham group 50.05 (13.97). Gender (M:F): 29 men / 13 women (analysed). Ethnicity: Not stated.
Further population details	1. Mild hearing loss: Not applicable 2. People with learning disability or cognitive impairment: Not applicable 3. Profoundly deaf: Not applicable
Indirectness of population	No indirectness
Interventions	(n=26) Intervention 1: Neuromodulation - Repetitive transcranial magnetic stimulation (rTMS) . Repetitive TMS was administered according to current safety guidelines (Wasserman 1998). The Magstim Super Rapid (Magstim Company Ltd., Whitland, UK) stimulator was used for stimulation. Active and sham rTMS was delivered through a figure-eight coil. Sham stimulation was carried out by tilting the coil 45 degrees away from the skull. The treatment group received real stimulation, 2 x 5 sessions, 1 Hz rTMS, stimulation intensity 110% of the individual resting motor threshold, 1500 stimuli per session, coil position over the left primary auditory cortex (Broadmann areas 41 and 42) localized and marked by a water-resistant pen during Brainsight stereotaxy navigation session. Patients were enrolled in the study on Monday and received five sessions of rTMS on five consecutive business days. In both groups, low frequency rTMS was administered over the left auditory cortex regardless of tinnitus laterality. During both types of treatments, the coil was held by a mechanical arm and the correct position was periodically adjusted by a physician who was present during the stimulation session. Duration 5 days (5 sessions). Concurrent medication/care: Inclusion criteria: pharmacological treatment for at least 3 months without significant clinical response, identical doses of current pharmacological treatment for at least 6 weeks. Indirectness: No indirectness

	(n=26) Intervention 2: Control group - Sham/placebo intervention. Repetitive TMS was administered according to current safety guidelines (Wasserman 1998). The Magstim Super Rapid (Magstim Company Ltd., Whitland, UK) stimulator was used for stimulation. Active and sham rTMS was delivered through a figure-eight coil. Sham stimulation was carried out by tilting the coil 45 degrees away from the skull. The control group received sham stimulation by distortion of the magnetic coil 45 degrees away from the skull with one wing touching the skull. The placement, coil position and stimulation parameters were as in the treatment group. . Duration 5 days (5 sessions). Concurrent medication/care: Inclusion criteria: pharmacological treatment for at least 3 months without significant clinical response, identical doses of current pharmacological treatment for at least 6 weeks.. Indirectness: No indirectness
Funding	Academic or government funding (Supported by research grants IGA MZCR NR/8805-4 and MSM 0021620849.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (RTMS) versus SHAM/PLACEBO INTERVENTION

Protocol outcome 1: Tinnitus severity
- Actual outcome: Tinnitus Handicap Inventory (THI) at Post-treatment; Group 1: mean 31.82 (SD 22.9); n=22, Group 2: mean 23.1 (SD 19.5); n=20; Tinnitus Handicap Inventory (THI) 0-100 Top=High is poor outcome; Comments: Baselines, mean (SD):
Active rTMS group 37.09 (21.7)
Sham rTMS group 23.1 (19.5)
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: THI baselines, mean (SD):
Active rTMS 37.09 (21.7)
Sham rTMS 26.5 (20.4); Group 1 Number missing: 4, Reason: Subjective worsening of tinnitus (n=2), unacceptable pain in stimulation area (n=1) and headache (n=1); Group 2 Number missing: 6, Reason: Lack of efficacy (n=3), headache (n=2) and not known (n=1)
- Actual outcome: Tinnitus Handicap Inventory (THI) at 26 week follow-up; Group 1: mean 33.27 (SD 21.6); n=22, Group 2: mean 27.7 (SD 23.2); n=20; Tinnitus Handicap Inventory (THI) 0-100 Top=High is poor outcome; Comments: Baselines, mean (SD):
Active rTMS group 37.09 (21.7)
Sham rTMS group 23.1 (19.5)
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: THI baselines, mean (SD):
Active rTMS 37.09 (21.7)
Sham rTMS 26.5 (20.4); Group 1 Number missing: 4, Reason: Subjective worsening of tinnitus (n=2), unacceptable pain in stimulation area (n=1) and

	headache (n=1); Group 2 Number missing: 6, Reason: Lack of efficacy (n=3), headache (n=2) and not known (n=1) - Actual outcome: Goebel & Hiller tinnitus questionnaire (total score) at Post-treatment; Group 1: mean 27.77 (SD 17.51); n=22, Group 2: mean 20.65 (SD 16.28); n=20; Goebel & Hiller Tinnitus Questionnaire 0-84 Top=High is poor outcome; Comments: Baselines, mean (SD): Active rTMS group 31.5 (16.28) Sham rTMS group 22.65 (15.13) Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Baselines, mean (SD): Active rTMS group 31.5 (16.28) Sham rTMS group 22.65 (15.13); Group 1 Number missing: 4, Reason: Subjective worsening of tinnitus (n=2), unacceptable pain in stimulation area (n=1) and headache (n=1); Group 2 Number missing: 6, Reason: Lack of efficacy (n=3), headache (n=2) and not known (n=1) - Actual outcome: Goebel & Hiller tinnitus questionnaire (total score) at 26 week follow-up; Group 1: mean 28.73 (SD 18.74); n=22, Group 2: mean 23.9 (SD 18.41); n=20; Goebel & Hiller Tinnitus Questionnaire 0-84 Top=High is poor outcome; Comments: Baselines, mean (SD): Active rTMS group 31.5 (16.28) Sham rTMS group 22.65 (15.13) Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Baselines, mean (SD): Active rTMS group 31.5 (16.28) Sham rTMS group 22.65 (15.13); Group 1 Number missing: 4, Reason: Subjective worsening of tinnitus (n=2), unacceptable pain in stimulation area (n=1) and headache (n=1); Group 2 Number missing: 6, Reason: Lack of efficacy (n=3), headache (n=2) and not known (n=1)
Protocol outcomes not reported by the study	Tinnitus distress ; Tinnitus annoyance ; Health-related quality of life ; Tinnitus-related quality of life ; Tinnitus loudness ; Depression ; Anxiety ; Anxiety and depression ; Sleep ; Adverse events: safety ; Adverse events: tolerability/adherence/drop-outs/attrition ; Adverse events: side effects (e.g. worsening of tinnitus)

Study	Bilici 2015[3]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=45)
Countries and setting	Conducted in Turkey; Setting:
Line of therapy	Unclear
Duration of study	Intervention + follow up: 2 weeks + 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Unilateral or bilateral moderate-to-severe tinnitus continuing for at least 1 year, a Tinnitus Handicap Inventory (THI) total score above 38 (Level 3, 4, 5), a Tinnitus Severity Index (TSI) total score above 36, normal hearing level, no previous rTMS treatment history, no antidepressant or tinnitus drugs usage for the past year.
Exclusion criteria	All participants underwent otologic examinations and any patients with middle ear disease were excluded from the study. Cranial magnetic resonance imaging (MRI) was also performed in all participants to exclude anyone with intracranial lesions from the study. Middle ear disease, presence of an intracranial lesion, hearing loss, presence of an intracranial lesion, hearing loss, presence of systemic illness, any contraindication to rTMS exposure, patient rTMS refusal, communication problems, cardiac pacemaker, electronic implants, gestation or lactation, epilepsy or syncope history, chronic alcohol consumption, or any drug usage compromising cognitive functions. The patients whose Beck Anxiety Scoring (BAS) and Psychiatric Sign Screening (PSS) test scores were abnormal were excluded from the study; therefore, no included patient had anxiety syndrome or depression.
Age, gender and ethnicity	Age - Mean (SD): 40 (13.2). Gender (M:F): 33 male / 42 female. Ethnicity: Not stated.

Further population details	1. Mild hearing loss: Not applicable 2. People with learning disability or cognitive impairment: Not applicable 3. Profoundly deaf: Not applicable
Indirectness of population	--
Interventions	(n=15) Intervention 1: Neuromodulation - Repetitive transcranial magnetic stimulation (rTMS). rTMS at 1 Hz frequency. A neuro-MS magnetic stimulator with a large circular coil (trade name Neurosoft) was used. For each 15 minute session of 1 Hz rTMS, 900 stimuli were applied at an intensity of 110% resting motor threshold. Patients received stimulation on ten subsequent days. Stimulation was applied via a coil placed close to the left temporoparietal region, independent of the side of the tinnitus, as described by Khedr et al. Duration 2 weeks. Concurrent medication/care: None stated. Indirectness: No indirectness (n=15) Intervention 2: Neuromodulation - Repetitive transcranial magnetic stimulation (rTMS) . rTMS at 10 Hz frequency. A neuro-MS magnetic stimulator with a large circular coil (trade name Neurosoft) was used. For each 15 minute 10 Hz rTMS session, 600 stimuli were applied as 20 trains of 30 stimuli (inter-train interval of 25 seconds) at an intensity of 110% resting motor threshold. Patients received stimulation on ten subsequent days. Stimulation was applied via a coil placed close to the left temporoparietal region, independent of the side of the tinnitus, as described by Khedr et al. . Duration 2 weeks. Concurrent medication/care: None stated. Indirectness: No indirectness (n=15) Intervention 3: Control group - Sham/placebo intervention. Placebo stimulation was performed with a sham coil system that mimicked the sound of active stimulation, without producing a magnetic field.. Duration 2 weeks. Concurrent medication/care: None stated.. Indirectness: No indirectness
Funding	Funding not stated (Stated that none of the authors has any financial disclosures or commercial associations that might pose or create a conflict of interest with the information presented.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (RTMS) versus SHAM/PLACEBO INTERVENTION

Protocol outcome 1: Tinnitus severity
- Actual outcome: 1 Hz rTMS. Tinnitus Handicap Index at Post-treatment (1 month); Group 1: mean -18 (SD 21); n=15, Group 2: mean 0.7 (SD 5); n=15
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

- Actual outcome: 1 Hz rTMS. Tinnitus Handicap Index at 6 months; Group 1: mean -17.7 (SD 22.4); n=15, Group 2: mean 0.7 (SD 5); n=15
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome: 1 Hz rTMS. Tinnitus Severity Index at Post-treatment (1 month); Group 1: mean -4.3 (SD 6.7); n=15, Group 2: mean -0.6 (SD 4.9); n=15
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome: 1 Hz rTMS. Tinnitus Severity Index at 6 months; Group 1: mean -3.7 (SD 11.4); n=15, Group 2: mean 1.1 (SD 6.3); n=15
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome: 10 Hz rTMS. Tinnitus Handicap Index at Post-treatment (1 month); Group 1: mean -9.1 (SD 8.8); n=15, Group 2: mean 0.7 (SD 5); n=15
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome: 10 Hz rTMS. Tinnitus Handicap Index at 6 months; Group 1: mean -15.2 (SD 11.7); n=15, Group 2: mean 0.7 (SD 5); n=15
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome: 10 Hz rTMS. Tinnitus Severity Index at Post-treatment (1 month); Group 1: mean -2.1 (SD 5.1); n=15, Group 2: mean -0.6 (SD 4.9); n=15
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing; Group 2 Number missing:
- Actual outcome: 10 Hz rTMS. Tinnitus Severity Index at 6 months; Group 1: mean -6.7 (SD 5.9); n=15, Group 2: mean 1.1 (SD 6.3); n=15
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing; Group 2 Number missing:

Protocol outcome 2: Anxiety
- Actual outcome: 1 Hz rTMS. Beck Anxiety Score at Post-treatment (1 month); Group 1: mean 10.5 (SD 9); n=15, Group 2: mean 13 (SD 9.5); n=15; Beck Anxiety Inventory 0-63 Top=High is poor outcome; Comments: Baselines, mean (SD):
1 Hz rTMS group 12.1 (11.1)
Control group 13.0 (9.6)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome: 1 Hz rTMS. Beck Anxiety Score at 6 months; Group 1: mean 10.3 (SD 8.3); n=15, Group 2: mean 14.1 (SD 10.2); n=15; Beck Anxiety Inventory 0-63 Top=High is poor outcome; Comments: Baselines, mean (SD):
1 Hz rTMS group 12.1 (11.1)
Control group 13.0 (9.6)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome: 10 Hz rTMS. Beck Anxiety Score at Post-treatment (1 month); Group 1: mean 15.3 (SD 8.7); n=15, Group 2: mean 13 (SD 9.5); n=15; Beck Anxiety Inventory 0-63 Top=High is poor outcome; Comments: Baselines, mean (SD):

10 Hz rTMS group 15.9 (9.4) Control group 13.0 (9.6) Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: 10 Hz rTMS. Beck Anxiety Score at 3 months; Group 1: mean 15 (SD 7.9); n=15, Group 2: mean 14.1 (SD 10.2); n=15; Beck Anxiety Inventory 0-63 Top=High is poor outcome; Comments: Baselines, mean (SD): 10 Hz rTMS group 15.9 (9.4) Control group 13.0 (9.6) Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Tinnitus distress; Tinnitus annoyance; Health-related quality of life; Tinnitus-related quality of life; Tinnitus loudness; Depression; Anxiety and depression; Sleep; Adverse events: safety; Adverse events: tolerability/adherence/drop-outs/attrition; Adverse events: side effects (e.g. worsening of tinnitus)

Study	Chung 2012[5]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=22)
Countries and setting	Conducted in China; Setting: China Medical University Hospital
Line of therapy	Unclear
Duration of study	Intervention + follow up: 10 days + 1 month
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: conducted otologic examinations, including pure-tone audiometry (PTA), auditory brainstem response (ABR), and tinnitus frequency- and loudness-matching tests.
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Right-handed tinnitus sufferers whose symptoms had not resolved with medication or other adjuvant treatments such as acupuncture and retraining therapy. To be included in this study, patients had to clarify the exact pitch and intensity of their tinnitus so that we could determine whether there had been audiological shifts in tinnitus frequency and loudness after rTMS.
Exclusion criteria	Subjects with narrow band, white or pink tinnitus were not included in this clinical trial. Patients with a known history of metal implantation, head injury, stroke, or epilepsy were excluded from this study.
Age, gender and ethnicity	Age - Mean (SD): Active rTMS group 53.83 (18.4) ; Sham rTMS group 51.9 (15.5). Gender (M:F): 20 male, 2 female. Ethnicity: Not stated.
Further population details	1. Mild hearing loss: People with hearing loss (Eight patients had normal hearing thresholds, 5 patients had downward-sloping sensorineural hearing loss, 4 patients had high-tone sensorineural hearing loss, 3 patients had low-tone hearing loss, and 2 patients had trough-shaped sensorineural hearing loss.). 2. People with learning disability or cognitive impairment: People without learning disability or cognitive impairment 3. Profoundly deaf: Not profoundly deaf

Extra comments	The study group included patients with tinnitus in 1 ear (17 individuals) and in both ears (5 individuals). All patients had experienced symptoms for at least 6 months (range 6 months to 20 years).
Indirectness of population	No indirectness
Interventions	(n=12) Intervention 1: Neuromodulation - Repetitive transcranial magnetic stimulation (rTMS) . The rTMS was applied using a figure-eight-shaped coil (Magstim SuperRapid; The Magstim Company Ltd., Whitland, UK). The resting motor threshold (RMT) was the basic intensity of proper rTMS dosing. In order to determine this value, the coil was placed approximately 5 cm above the left auricle and rotated around the horizontal axis, after which the handle of the coil was pointing backwards, approximately 45° from the mid-sagittal line. In the active-stimulation group, the coil was placed over the targeted region with the intensity setting at 80% of the RMT. Continuous theta-burst rTMS (cTBS) was delivered at a burst frequency of 5 Hz (the theta rhythm in the EEG); each burst consisted of 3 pulses repeated at 50 Hz. We administered 900 pulses (300 bursts) of stimulation once daily for 10 consecutive business days. Duration 10 days (10 sessions). Concurrent medication/care: Not specified. Indirectness: No indirectness (n=10) Intervention 2: Control group - Sham/placebo intervention. The sham-stimulation group patients received an identical protocol to the active-stimulation group, but with the sham coil (The Magstim Company Ltd.). After completing the rTMS treatment, each patient was subjected to a second round of evaluation testing and asked to respond to the TQ and THI at 1 week and at 1 month after treatment. Duration 10 days (10 sessions). Concurrent medication/care: Not specified. Indirectness: No indirectness
Funding	Academic or government funding (This research was supported by research grants from China Medical University (CMU98-NTU-13), China Medical University Hospital (DMR97-064, DMR97-147, DMR100-043, DMR-100-045, CTC-99-009); the Clinical Trial and Research Center of Excellence Funds (DOH100-TD-B-111-004) and the National Science Council (NSC 99-2314-B-039-016-MY2) from Taiwan Department of Health.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (RTMS) versus SHAM/PLACEBO INTERVENTION

Protocol outcome 1: Tinnitus severity
- Actual outcome: Tinnitus severity on Tinnitus Handicap Inventory (THI) at 1 week post-treatment (3 weeks); Group 1: mean -8.33 (SD 7.9); n=12, Group 2: mean 0 (SD 4.22); n=10; Tinnitus Handicap Inventory 0-100 Top=High is poor outcome

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Tinnitus severity on Tinnitus Handicap Inventory (THI) at 1 month post-treatment (6 weeks); Group 1: mean -5.33 (SD 8.24); n=12, Group 2: mean 0 (SD 3.27); n=10; Tinnitus Handicap Inventory 0-100 Top=High is poor outcome Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Tinnitus severity on Tinnitus Questionnaire at 1 week post-treatment (3 weeks); Group 1: mean -8.58 (SD 7.57); n=12, Group 2: mean 0.1 (SD 3.18); n=10; Tinnitus Questionnaire (TQ) 0-82 Top=High is poor outcome Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Tinnitus severity on Tinnitus Questionnaire at 1 month post-treatment (6 weeks); Group 1: mean -4 (SD 6.42); n=12, Group 2: mean 0.2 (SD 2.62); n=10; Tinnitus Questionnaire (TQ) 0-82 Top=High is poor outcome Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Tinnitus distress; Tinnitus annoyance; Health-related quality of life; Tinnitus-related quality of life; Tinnitus loudness; Depression; Anxiety; Anxiety and depression; Sleep; Adverse events: safety; Adverse events: tolerability/adherence/drop-outs/attrition; Adverse events: side effects (e.g. worsening of tinnitus)

Study	Folmer 2015[9]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=70)
Countries and setting	Conducted in USA; Setting: Not stated.
Line of therapy	Unclear
Duration of study	Intervention + follow up: 10 days + 26 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Individuals were formally assessed for eligibility via questionnaires, cognitive test and physical examination.
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Individuals who experience chronic tinnitus, 18 years old and over, hadn't previously experienced TMS, hadn't had any other tinnitus treatment or management programs for four weeks prior to the study. All degrees of hearing function were included, recognizing that participants with profound, bilateral losses would not be able to perform tinnitus evaluations and hearing tests, but would be able to rate subjective tinnitus loudness, annoyance and impact on life. Tinnitus duration of 1 year or more, constant tinnitus (no intermittence or variation), self-rated tinnitus loudness of 6 or greater on a 0-10 scale.
Exclusion criteria	Score of below 24 on the Mini-Mental State Examination, to exclude individuals with dementia or other forms of cognitive impairment. Other exclusion criteria: objective tinnitus; history of seizures or epileptic activity; history or evidence of significant brain malformation or neoplasm; cerebral vascular events (such as strokes); prior brain surgery; cardiac pace makers; other electronic implants (including cochlear implants); intracranial or intraocular metallic particles; drugs that might reduce the seizure threshold; pregnancy.

Recruitment/selection of patients	Participants were recruited from the Portland (Oregon) metropolitan area and were paid $20for each appointment they attended, which included the initial appointment, each of the rTMSsessions, and each of the follow-up appointments.
Age, gender and ethnicity	Age - Mean (SD): 60.6 (8.9). Gender (M:F): 51 men / 13 women (analysed). Ethnicity: Not stated
Further population details	1. Mild hearing loss: Not applicable 2. People with learning disability or cognitive impairment: Not applicable 3. Profoundly deaf: Not applicable
Indirectness of population	No indirectness
Interventions	(n=35) Intervention 1: Neuromodulation - Repetitive transcranial magnetic stimulation (rTMS) . 16 subjects received 2000 pulses of active rTMS on the left side of the head during daily sessions for 10 consecutive working days. Stimulation rate: 1 Hz; stimulation intensity; 110% of the individual resting motor threshold or lower, with the figure-of-eight coil positioned over left auditory cortex. The coil was placed in an adjustable stand that held it against the subject's head in a fixed location. During rTMS sessions, subjects say in a comfortable chair with head and neck supports which helped them to minimize movements. The active rTMS coil was positioned on the subject's scalp using a 10-20 EEG-system that has demonstrated ability to place the coil over auditory cortex without the need of using magnetic resonance or positron emission tomography (PET) guidance. A second subgroup of 16 subjects received active rTMS on the right side of the head during daily sessions for 10 consecutive work days, 1 Hz rTMS, stimulation intensity 110% or lower related to the individual resting motor threshold, with the figure-of-eight coil positioned over right auditory cortex. Procedures for determining resting motor threshold (rMT) were the same as described above, but the TMS coil was positioned over right motor cortex and skin surface electrodes were placed on the left hand. Prior to both active and sham rTMS, the study audiologist inserted foam ear plugs into the participants' ear canals to minimize the effects of rTMS sounds on their hearing threshold and tinnitus. Ear plugs were not worn during VNS loudness assessments that took place before and after each TMS session.. Duration 10 sessions over 2 weeks. Concurrent medication/care: Participants were required not to have been involved in any tinnitus treatment or management for four weeks before enrolling in the study.. Indirectness: No indirectness (n=35) Intervention 2: Control group - Sham/placebo intervention. The placebo coil was identical in appearance to the active coil and produced sounds and scalp sensations that were similar to those produced by the active coil. The manufacturer (Magstim Company Ltd) asserts that the placebo coil contains a metal plate that blocks much of the magnetic field it generates from affecting neural activity. As in the active rTMS group, participants were randomized to 1 of 2 subgroups containing 16 participants

	each: 1. sham rTMS on the left side of the head and 2. sham rTMS on the right side of the head. Prior to both active and sham rTMS, the study audiologist inserted foam ear plugs into the participants' ear canals to minimize the effects of rTMS sounds on their hearing threshold and tinnitus. Ear plugs were not worn during VNS loudness assessments that took place before and after each TMS session.. Duration 10 sessions over 2 weeks. Concurrent medication/care: Participants were required not to have been involved in any tinnitus treatment or management for four weeks before enrolling in the study.. Indirectness: No indirectness
Funding	Academic or government funding (This research was supported by a grant from the US Department of Veterans Affairs Rehabilitation Research and Development Service. Additional support was provided by the Veterans Affairs National Center for Rehabilitative Auditory Research at Portland Veterans Affairs Medical Center.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (RTMS) versus SHAM/PLACEBO INTERVENTION

Protocol outcome 1: Tinnitus severity
- Actual outcome: Tinnitus Functional Index (TFI) change from baseline at Post-treatment; Group 1: mean -5.2 (SD 11.8); n=32, Group 2: mean -1.8 (SD 10.5); n=32; Tinnitus Functional Index (TFI) 0-100 Top=High is poor outcome; Comments: Baselines, mean (SD):
Sham rTMS group 40.6 (22.2)
Active rTMS group 44.8 (19.4)
Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 1 did not receive intervention as randomized; 2 discontinued intervention due to personal reasons.; Group 2 Number missing: 3, Reason: 1 did not receive intervention as randomized; 1 discontinued intervention due to personal reasons; 1 lost to follow-up due to suspected drug abuse.
- Actual outcome: Tinnitus Functional Index (TFI) change from baseline at 26 weeks follow-up; Group 1: mean -13.8 (SD 15.2); n=32, Group 2: mean -2.9 (SD 15.8); n=32; Tinnitus Functional Index (TFI) 0-100 Top=High is poor outcome; Comments: Baselines, mean (SD):
Sham rTMS group 40.6 (22.2)
Active rTMS group 44.8 (19.4)
Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 1 did not receive intervention as randomized; 2 discontinued intervention due to personal reasons.; Group 2 Number missing: 3, Reason: 1 did not receive intervention as randomized; 1 discontinued intervention due to personal reasons; 1 lost to follow-up due to suspected drug abuse.

Protocol outcomes not reported by the study	Tinnitus distress; Tinnitus annoyance; Health-related quality of life; Tinnitus-related quality of life; Tinnitus loudness; Depression; Anxiety; Anxiety and depression; Sleep; Adverse events: safety; Adverse events: tolerability/adherence/drop-outs/attrition; Adverse events: side effects (e.g. worsening of tinnitus)

Study	**Formanek 2018[10]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=32)
Countries and setting	Conducted in Czech Republic; Setting: Not specified.
Line of therapy	Unclear
Duration of study	Intervention + follow up: 5 days + 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: The definition of tinnitus was based on subjective complaints of noise, ringing, and/or buzzing with no external source.
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Not specified.
Exclusion criteria	Not specified.
Recruitment/selection of patients	Not specified.
Age, gender and ethnicity	Age - Mean (SD): rTMS group 47.9 (14.31) ; Sham group 51.8 (10.34). Gender (M:F): Define. Ethnicity: Not stated.
Further population details	1. Mild hearing loss: Not stated / Unclear 2. People with learning disability or cognitive impairment: Not stated

	/ Unclear 3. Profoundly deaf: Not stated / Unclear
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Neuromodulation - Repetitive transcranial magnetic stimulation (rTMS) . rTMS 1 Hz + rTMS 25 Hz (combined) The DuoMAG XT-100 transcranialmagnetic stimulator (Deymed, Payette, ID, USA) was used for magnetic stimulation. The rTMS was performed with a 70-mm air-cooled 70BF Butterfly Coil(Deymed). The resting motor threshold (RMT) was determined in every rTMSpatient on the first day of treatment using a descending staircase method until the lowest intensity at which 5 of 10 consecutive pulses induced a visible twitch in the contralateral hand was reached. For each hemisphere, the intensity was set according to the motor threshold obtained for that hemisphere. The dorsolateral prefrontal cortex (frequency 25 Hz, 300 pulses, and 80% RMT) on the left side and primary auditory cortex on both sides (1 Hz,1000 pulses, and 110% RMT) were stimulated in every patient for 5 consecutive days. There was no difference between rTMS group and sham stimulation group. Every patient received 2300 pulses per session (three stimulation sites). A5–10 min break was used to switch the coil from one position to the other and to allow the patient to relax. All patients were treated by the same investigator.. Duration 5 sessions over 5 days. Concurrent medication/care: Not stated/unclear.. Indirectness: No indirectness (n=12) Intervention 2: Control group - Sham/placebo intervention. Placebo treatment was performed with a 70-mm 70BFP Placebo Butterfly Coil (Deymed) replicating the appearance, sound emission, stimulation of superficial tissue (muscles), and operation of the TMS coil without stimulating the cortical tissue. Motor thresholds were not determined in placebo patients to prevent them from perceiving the difference between real and placebo TMS, protecting the blinding. The neuronavigation procedure and treatment schedule were similar.. Duration 5 sessions over 5 days. Concurrent medication/care: Unclear/not stated.. Indirectness: No indirectness
Funding	Academic or government funding (Supported by Ministry of Health, Czech Republic – conceptual development of research organization (FNOs/2015).)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (RTMS) versus SHAM/PLACEBO INTERVENTION	

Protocol outcome 1: Tinnitus severity - Actual outcome for Adults: Tinnitus Handicap Inventory (THI) at 1 month follow-up; Group 1: mean 4.5 (SD 11.72); n=19, Group 2: mean 0.2 (SD 7.98); n=12; Comments: Positive value means tinnitus improvement. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Lost to follow-up; Group 2 Number missing: 0 - Actual outcome for Adults: Tinnitus Handicap Inventory (THI) at 6 month follow-up; Group 1: mean 9.1 (SD 11.85); n=20, Group 2: mean 4.3 (SD 9.41); n=12; Comments: Positive value means tinnitus improvement. Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Adults: Tinnitus Handicap Questionnaire (THQ) at 1 month follow-up; Group 1: mean 1.5 (SD 8.52); n=19, Group 2: mean -1.1 (SD 8.75); n=12; Comments: Positive value means tinnitus improvement. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Lost to follow-up; Group 2 Number missing: 0 - Actual outcome for Adults: Tinnitus Handicap Questionnaire (THQ) at 6 month follow-up; Group 1: mean 6.1 (SD 12.55); n=20, Group 2: mean 2.8 (SD 6.34); n=12; Comments: Positive value means tinnitus improvement. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Depression - Actual outcome for Adults: Beck Depression Inventory (BDI) at 1 month follow-up; Group 1: mean 0.5 (SD 4.4); n=19, Group 2: mean -0.6 (SD 4.29); n=12; Comments: Positive value means tinnitus improvement. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Lost to follow-up; Group 2 Number missing: 0 - Actual outcome for Adults: Beck Depression Inventory (BDI) at 6 month follow-up; Group 1: mean 0.1 (SD 5.5); n=20, Group 2: mean 0 (SD 3.59); n=12; Comments: Positive value means tinnitus improvement. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Note: for all of the above, participant loss to follow-up for each outcome at one month follow-up is unclear.	
Protocol outcomes not reported by the study	Tinnitus distress; Tinnitus annoyance; Health-related quality of life; Tinnitus-related quality of life; Tinnitus loudness; Anxiety; Anxiety and depression; Sleep; Adverse events: safety; Adverse events: tolerability/adherence/drop-outs/attrition; Adverse events: side effects (e.g. worsening of tinnitus)

Study	Forogh 2016[11]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=22)
Countries and setting	Conducted in Iran; Setting: Not stated.
Line of therapy	Unclear
Duration of study	Intervention + follow up: 5 days + 2 weeks
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients over age of 18 with chronic tinnitus for at least 6 months.
Exclusion criteria	Fluctuating audition, Meniere disease, history of traumatic brain injury, epilepsy, intake of ototoxic, antipsychotic and antiepileptic medications, tricyclic antidepressants or benxodiazepines within 1 month prior to the study, previous experience of receiving tDCS, cochlear implants, cardiac pacemakers and pregnancy.
Recruitment/selection of patients	Not stated.
Age, gender and ethnicity	Age - Mean (range): 48.22 (26-80). Gender (M:F): 14 male / 8 female. Ethnicity: Not stated.
Further population details	1. Mild hearing loss: Not applicable 2. People with learning disability or cognitive impairment: Not applicable 3. Profoundly deaf: Not applicable

Indirectness of population	No indirectness
Interventions	(n=11) Intervention 1: Neuromodulation - Transcranial direct current stimulation (tDCS). The anode electrode was positioned over left temporoparietal area located halfway between C3 and T5 using international 10-20 electroencephalogram system. The cathode electrode was placed over right supraorbital area. Direct electrical current was generated by a battery-driven direct current stimulator (Activadose II) with a maximum current output of 4mA and was transmitted through two pairs of 35 CM2 rubber electrodes covered with 0.9% saline soaked sponges. The direct current was ramped up to 2.0 mA within 30 seconds. Patients in the tDCS group received 20 minutes of stimulation with a current intensity of 2 mA. The ramp-down time was 4 seconds. The stimulator was placed behind and out of sight of the patients.. Duration 5 sessions (5 days). Concurrent medication/care: Patients were required not to be taking ototoxic, antipsychotic and antiepileptic medications, tricyclic antidepressants or benxodiazepines within 1 month prior to the study.. Indirectness: No indirectness (n=11) Intervention 2: Control group - Sham/placebo intervention. The sham tDCS control group were set up in the same way as the active tDCS group. However, after the direct current was ramped up to 2.0 mA within 30 seconds. However, after the initial ramp-up, the current was directly ramped down to 9, so patients felt a tingling sensation at the beginning and received no more stimulation in the remaining time of the session. The ramp-down time was 4 seconds. The stimulator was placed behind and out of sight of the patients.. Duration 5 sessions (5 days). Concurrent medication/care: Patients were required not to be taking ototoxic, antipsychotic and antiepileptic medications, tricyclic antidepressants or benxodiazepines within 1 month prior to the study.. Indirectness: No indirectness
Funding	Funding not stated (Authors declare no conflict of interests.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS) versus SHAM/PLACEBO INTERVENTION

Protocol outcome 1: Tinnitus severity
- Actual outcome for Adults: Tinnitus handicap inventory (THI) at Post-treatment; Group 1: mean 58.6 (SD 28.1); n=10, Group 2: mean 54.1 (SD 24.9); n=10; Tinnitus handicap inventory (THI) 0-100 Top=High is poor outcome; Comments: Baselines, mean (SD):
Active tDCS group 58.6 (28.1)
Sham tDCS group 53.7 (20.0)

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Worsening of tinnitus after the first session; Group 2 Number missing: 1, Reason: Personal reasons
- Actual outcome for Adults: Tinnitus handicap inventory (THI) at 2 week follow-up; Group 1: mean 55.8 (SD 23.2); n=10, Group 2: mean 53.4 (SD 30.9); n=10; Tinnitus handicap inventory (THI) 0-100 Top=High is poor outcome; Comments: Baselines, mean (SD):
Active tDCS group 58.6 (28.1)
Sham tDCS group 53.7 (20.0)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Worsening of tinnitus after the first session; Group 2 Number missing: 1, Reason: Personal reasons

Protocol outcome 2: Tinnitus distress
- Actual outcome for Adults: Tinnitus distress on visual analogue scale (VAS) at Post-treatment; Group 1: mean 5 (SD 2.1); n=10, Group 2: mean 4.5 (SD 1.9); n=10; Visual analogue scale (VAS) 0-10 Top=High is poor outcome; Comments: Baselines, mean (SD):
Active tDCS 5.6 (2.5)
Sham tDCS 4.7 (2.3)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Worsening of tinnitus after the first session; Group 2 Number missing: 1, Reason: Personal reasons
- Actual outcome for Adults: Tinnitus distress on visual analogue scale (VAS) at 2 week follow-up; Group 1: mean 5 (SD 2.2); n=10, Group 2: mean 4.2 (SD 2.4); n=10; Visual analogue scale (VAS) 0-10 Top=High is poor outcome; Comments: Baselines, mean (SD):
Active tDCS 5.6 (2.5)
Sham tDCS 4.7 (2.3)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Worsening of tinnitus after the first session; Group 2 Number missing: 1, Reason: Personal reasons

Protocol outcome 3: Tinnitus loudness
- Actual outcome for Adults: Tinnitus loudness on visual analogue scale (VAS) at Post-treatment; Group 1: mean 4.8 (SD 2.2); n=10, Group 2: mean 5 (SD 2.4); n=10; Visual analogue scale (VAS) 0-10 Top=High is poor outcome; Comments: Baselines, mean (SD):
Active tDCS 5.3 (2.6)
Sham tDCS 5.2 (2.5)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Worsening of tinnitus after the first session; Group 2 Number missing: 1, Reason: Personal reasons

- Actual outcome for Adults: Tinnitus loudness on visual analogue scale (VAS) at 2 week follow-up; Group 1: mean 5.1 (SD 2.5); n=10, Group 2: mean 4.8 (SD 2.8); n=10; Visual analogue scale (VAS) 0-10 Top=High is poor outcome; Comments: Baselines, mean (SD): Active tDCS 5.3 (2.6) Sham tDCS 5.2 (2.5) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Worsening of tinnitus after the first session; Group 2 Number missing: 1, Reason: Personal reasons	
Protocol outcomes not reported by the study	Tinnitus annoyance; Health-related quality of life; Tinnitus-related quality of life; Depression; Anxiety; Anxiety and depression; Sleep; Adverse events: safety; Adverse events: tolerability/adherence/drop-outs/attrition; Adverse events: side effects (e.g. worsening of tinnitus)

Study	Ghossaini 2004[14]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=37)
Countries and setting	Conducted in USA; Setting: An urban otology practice.
Line of therapy	Unclear
Duration of study	Intervention time: 1 month
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Chronic tinnitus for at least 6 months. Tinnitus annoyance at a level to motivate them to seek treatment.
Exclusion criteria	None specified.
Recruitment/selection of patients	Not stated.
Age, gender and ethnicity	Age - Range: 23-83 years old. Gender (M:F): Define. Ethnicity: Not stated.
Further population details	1. Mild hearing loss: Not stated / Unclear 2. People with learning disability or cognitive impairment: Not stated / Unclear 3. Profoundly deaf: Not stated / Unclear
Extra comments	Duration of tinnitus ranged from 7 months to 60 years. Twenty patients had bilateral and 17 patients had unilateral tinnitus. The cause or origin of tinnitus in the study sample varied. All patients had failed various treatment protocols to control their tinnitus. All patients met a threshold of annoyance in that they expressed motivation for tinnitus treatment requiring multiple visits..

Indirectness of population	No indirectness
Interventions	(n=18) Intervention 1: Neuromodulation - Repetitive transcranial magnetic stimulation (rTMS) . Very high-frequency rTMS (27 MHz) The active treatment device (Diapulse device model D103) was set to produce pulsed electromagnetic energy at a frequency of 27.12 MHz in 65-microsecond bursts with a repetition rate of 600 pulses per second at 975 W peak and a 6-inch penetration depth. Treatment was accomplished by placing the centre of the head of the unit approximately 1 inch lateral to the auricle, with signal delivered for 30 minutes. Patients with bilateral tinnitus received treatment to the ear with louder tinnitus. . Duration 30 minute sessions (3 times per week for 1 month). Concurrent medication/care: Unclear/not stated.. Indirectness: No indirectness (n=19) Intervention 2: Control group - Sham/placebo intervention. Patients in the placebo group were treated with a deactivated machine. Blinding was effective due to the fact that the active device emits a nonthermal, pulsed, high-frequency electromagnetic energy that could not be felt. Both active and placebo machines were identical in appearance, sounds, and presence of light when activated. . Duration 30 minute sessions (3 times per week for 1 month). Concurrent medication/care: Unclear/not stated.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (RTMS) versus SHAM/PLACEBO INTERVENTION

Protocol outcome 1: Tinnitus severity
- Actual outcome for Adults: Tinnitus Handicap Inventory at Post-treatment (1 month); Group 1: mean 29.43 (SD 23.58); n=14, Group 2: mean 37.33 (SD 22.37); n=15; Tinnitus Handicap Inventory 0-100 Top=High is poor outcome; Comments: Baselines, mean (SD):
rTMS group 33.78 (22.15)
Sham group 39.30 (22.55)
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference in THI baseline is larger than the treatment effect in the active rTMS group
Baselines, mean (SD):
rTMS group 33.78 (22.15)
Sham group 39.30 (22.55); Group 1 Number missing: 4, Reason: Dropped out before treatment began or did not return for post-treatment assessment.; Group 2 Number missing: 4, Reason: Dropped out before treatment began or did not return for post-treatment assessment.

- Actual outcome for Adults: Tinnitus Magnitude Rating (0-100 numeric scale equivalent to VAS) at Post-treatment (1 month); Group 1: mean 49.29 (SD 20.27); n=18, Group 2: mean 58.67 (SD 20.48); n=17; Tinnitus Magnitude Rating (equivalent to VAS) 0-100 Top=High is poor outcome; Comments: Baselines, mean (SD): rTMS group 51.11 (21.04) Sham group 59.38 (17.5) Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference in THI baseline is larger than the treatment effect in the active rTMS group Baselines, mean (SD): rTMS group 51.11 (21.04) Sham group 59.38 (17.5) ; Group 1 Number missing: 0; Group 2 Number missing: 2, Reason: Did not return for post-treatment assessment. Protocol outcome 2: Adverse events: side effects (e.g. worsening of tinnitus) - Actual outcome for Adults: Patient-reported (subjective) worsening of tinnitus at Post-treatment (1 month); Group 1: 4/18, Group 2: 5/19; Comments: Patients subjectively reported that their tinnitus worsened with the treatment. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Tinnitus distress; Tinnitus annoyance; Health-related quality of life; Tinnitus-related quality of life; Tinnitus loudness; Depression; Anxiety; Anxiety and depression; Sleep; Adverse events: safety; Adverse events: tolerability/adherence/drop-outs/attrition

Study	Landgrebe 2017[24]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=153 randomized)
Countries and setting	Conducted in Germany; Setting: Conducted at 7 centres: university ENT and psychiatric departments and 1 outpatient ENT clinic) in Germany from February 2008 to October 2011.
Line of therapy	Unclear
Duration of study	Intervention + follow up: 2 weeks + 24 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients (both sexes, age 18-70 years) with chronic tinnitus defined as a duration of at least 6 months with at least moderate severity defined as a screening sum score in the tinnitus handicap inventory (THI) of at least 38 points. Hearing levels had to be normal (age-adjusted, not more than 5 dB below the 10% percentile according to DIN EN ISO 7029) in all standard frequencies. In addition, conductive hearing loss was not allowed to be more severe than 15 dB. Patients had to be naive to rTMS to ensure blinding of the study.
Exclusion criteria	Objective tinnitus, simultaneous tinnitus-specific treatments, clinically relevant psychiatric comorbidity, especially diagnoses according to F1 to F3 main categories in the International Classification of diseases (ICD-10), simultaneous treatment with psychotropic agents (e.g. benzodiazepines, anticonvulsants, neuroleptics, antidepressants, but regular intake of hypnotics was permitted), severe instable somatic comorbidity, contraindications for rTMS, pregnancy and participation in a clinical trial within the last 30 days prior to study enrolment.
Age, gender and ethnicity	Age - Mean (SD): Real rTMS group 48.1 (12.5) ; sham rTMS group 49.9 (13.2). Gender (M:F): 105 male / 41 female (analysed). Ethnicity: Not stated.

Further population details	1. Mild hearing loss: Not applicable 2. People with learning disability or cognitive impairment: Not applicable 3. Profoundly deaf: Not applicable
Indirectness of population	No indirectness
Interventions	(n=75) Intervention 1: Neuromodulation - Repetitive transcranial magnetic stimulation (rTMS) . Patients randomized to real rTMS received two times 5 sessions (one session daily in two weeks) of 1-Hz-rTMS (2000 stimuli per session) applied to the left primary auditory cortex with a stimulation intensity of 110% related to the individual resting motor threshold. The left primary auditory cortex had been identified as a potential target region for the 1-Hz-rTMS -treatment of tinnitus in pilot studies. The position of the stimulation coil was defined using an algorithm based on the international standardized 10-20-EEG system. All study centres used TMS stimulators from Medtronic Co. (Denmark; MagPro X-100 or MagPro R30) with passively-cooled MCF-65 figure-of-eight coils. Duration 2 weeks (10 sessions). Concurrent medication/care: None stated. Exclusion of psychotropic agents eliminated as part of exclusion criteria. Indirectness: No indirectness (n=78) Intervention 2: Control group - Sham/placebo intervention. Patients in the sham group received the same treatment but the stimulation coil was tilted away from the skull by 45 degrees with one wing touching the skull (to ensure skin sensations induced by the magnetic impulse without inducing relevant biological activity. All study centres used TMS stimulators from Medtronic Co. (Denmark; MagPro X-100 or MagPro R30) with passively-cooled MCF-65 figure-of-eight coils.. Duration 2 weeks (10 sessions). Concurrent medication/care: None stated. Exclusion of psychotropic agents eliminated as part of exclusion criteria. Indirectness: No indirectness
Funding	Academic or government funding (The trial was funded by the German Research Foundation. As stated: 'the funding source had no influence on study design, data collection, analysis and interpretation of the data or writing of the report and the decision to submit the manuscript.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (RTMS) versus SHAM/PLACEBO INTERVENTION

Protocol outcome 1: Tinnitus severity
- Actual outcome: Tinnitus Questionnaire at Post-treatment; Group 1: mean 42.7 (SD 15.8); n=71, Group 2: mean 42.6 (SD 16.5); n=75; Tinnitus Questionnaire 0-84 Top=High is poor outcome; Comments: Baselines, mean (SD):
Real rTMS 43.1 (14.7)

Sham rTMS 42.1 (13.8)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 3
- Actual outcome: Tinnitus Questionnaire at 26 weeks; Group 1: mean 40.3 (SD 19.8); n=65, Group 2: mean 41.9 (SD 19.4); n=65; Tinnitus Questionnaire 0-84 Top=High is poor outcome; Comments: Baselines, mean (SD):
Real rTMS 43.1 (14.7)
Sham rTMS 42.1 (13.8)
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10; Group 2 Number missing: 13
- Actual outcome: Tinnitus Handicap Inventory (THI) at Post-treatment; Group 1: mean 50.2 (SD 21.3); n=71, Group 2: mean 49 (SD 20.2); n=75
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 3
- Actual outcome: Tinnitus Handicap Inventory (THI) at 26 week follow-up; Group 1: mean 45.5 (SD 25.5); n=65, Group 2: mean 47.1 (SD 22.5); n=66
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10; Group 2 Number missing: 12

Protocol outcome 2: Health-related quality of life
- Actual outcome: SF-12 Physical component at Post-treatment; Group 1: mean 47.8 (SD 7.3); n=70, Group 2: mean 47.5 (SD 8.3); n=73; SF-12 Physical component 0-100 Top=High is good outcome; Comments: Baselines, mean (SD):
Real rTMS 47.7 (8.2)
Sham rTMS 45.6 (8.1)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5; Group 2 Number missing: 5
- Actual outcome: SF-12 Physical component at 26 weeks; Group 1: mean 46.9 (SD 9.6); n=55, Group 2: mean 46.6 (SD 8.8); n=56; SF-12 Physical component 0-100 Top=High is good outcome; Comments: Baselines, mean (SD):
Real rTMS 47.7 (8.2)
Sham rTMS 45.6 (8.1)
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 20; Group 2 Number missing: 22
- Actual outcome: SF-12 Mental component at Post-treatment; Group 1: mean 47.1 (SD 10); n=70, Group 2: mean 48.1 (SD 10.6); n=73; SF-12 Mental component 0-100 Top=High is good outcome; Comments: Baselines, mean (SD):
Real rTMS 46.9 (10.5)
Sham rTMS 48.4 (9.8)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5; Group 2 Number missing: 5
- Actual outcome: SF-12 Mental component at 26 weeks; Group 1: mean 46.6 (SD 10.8); n=55, Group 2: mean 47.1 (SD 11.9); n=56; SF-12 Mental component 0-100 Top=High is good outcome; Comments: Baselines, mean (SD):
Real rTMS 46.9 (10.5)

Sham rTMS 48.4 (9.8) Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 20; Group 2 Number missing: 22 Protocol outcome 3: Depression - Actual outcome: Beck Depression Inventory at Post-treatment; Group 1: mean 8.1 (SD 6.6); n=71, Group 2: mean 7.7 (SD 5.9); n=75; Beck Depression Inventory (BDI) 0-63 Top=High is poor outcome; Comments: Baselines, mean (SD): Real rTMS 9.4 (7.2) Sham rTMS 8.5 (5.9) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 3 - Actual outcome: Beck Depression Inventory at 26 weeks; Group 1: mean 8.8 (SD 9.1); n=65, Group 2: mean 8.2 (SD 6.8); n=66; Beck Depression Inventory (BDI) 0-63 Top=High is poor outcome; Comments: Baselines, mean (SD): Real rTMS 9.4 (7.2) Sham rTMS 8.5 (5.9) Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10; Group 2 Number missing: 12	
Protocol outcomes not reported by the study	Tinnitus distress; Tinnitus annoyance; Tinnitus-related quality of life; Tinnitus loudness; Anxiety; Anxiety and depression; Sleep; Adverse events: safety; Adverse events: tolerability/adherence/drop-outs/attrition; Adverse events: side effects (e.g. worsening of tinnitus)

Study	Langguth 2014[25]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=96)
Countries and setting	Conducted in Germany
Line of therapy	Unclear
Duration of study	Intervention time: 10 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: All patients underwent complete ontological and audiological examination.
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 18-80 years, suffering from subjective tinnitus with duration of at least 3 months.
Exclusion criteria	Exclusion criteria were Morbus Meniere, conductive hearing loss, objective tinnitus, a history of seizures, a clinically relevant psychiatric comorbidity, a suspected diagnosis of organic brain damage, cardiac pacemakers or other electrical implants, pregnancy and prior treatment with rTMS.
Age, gender and ethnicity	Age - Mean (SD): Active group 44.9 (11.5), sham group 50.3 (12.9). Gender (M:F): 27 women, 65 men (analysed). Ethnicity:
Further population details	1. Mild hearing loss: Not stated / Unclear 2. People with learning disability or cognitive impairment: Not stated / Unclear 3. Profoundly deaf: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=48) Intervention 1: Neuromodulation - Repetitive transcranial magnetic stimulation (rTMS). PET-guided neuronavigated rTMS.

	Patients first underwent FDG-PET and MRI before being randomized. After fusion with structural MRI data the area of increased activation within the auditory cortices was chosen as the target for rTMS. The coil was positioned over this area by using a neuronavigational system with the handle of the coil pointing upwards. rTMS was applied with a figure-of-eight coil connected to a stimulator. Patients received stimulation on 10 subsequent working days. The rTMS protocol consisted of 2000 stimuli per session at a frequency of 1 Hz and an intensity of 110% motor threshold.. Duration 10 days. Concurrent medication/care: Not stated. Indirectness: No indirectness (n=48) Intervention 2: Control group - Sham/placebo intervention. For sham stimulation, a specific sham-coil system was used (90 mm outer diameter; coil MC-B70, Medtronic, Minneapolis, MN). Duration 10 days. Concurrent medication/care: Not stated.. Indirectness: No indirectness
Funding	Other (The study was funded by the Tinnitus Research Initiative.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (RTMS) versus SHAM/PLACEBO INTERVENTION Protocol outcome 1: Tinnitus severity - Actual outcome: Tinnitus Questionnaire at Post-treatment (10 days); Group 1: mean 1.88 (SD 5.62); n=44, Group 2: mean 0.76 (SD 5.55); n=47 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 1 Protocol outcome 2: Adverse events: side effects (e.g. worsening of tinnitus) - Actual outcome: Drop-out due to tinnitus worsening at Post-treatment (10 days); Group 1: 1/45, Group 2: 1/48; Comments: Started rTMS treatment but dropped out due to worsening of tinnitus. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 1	
Protocol outcomes not reported by the study	Tinnitus distress; Tinnitus annoyance; Health-related quality of life; Tinnitus-related quality of life; Tinnitus loudness; Depression; Anxiety; Anxiety and depression; Sleep; Adverse events: safety; Adverse events: tolerability/adherence/drop-outs/attrition

Study	Marcondes 2010[29]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=19)
Countries and setting	Conducted in Brazil
Line of therapy	Unclear
Duration of study	Intervention + follow up: 5 days + 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Uni- or bilateral tinnitus of at least 3 months duration, age over 18 years and normal pure tone audiometry (thresholds < 25 dB hearing level in all frequencies from 250 to 8000 Hz).
Exclusion criteria	Neurogenic or psychiatric disorders, especially epilepsy, migraine, depression, or anxiety, the intake of antidepressant, neuroleptic or anticonvulsant drugs, cardiac pacemaker or other implanted devices, intracranial metallic objects, pregnancy, and inability to fulfill the study requirements. Co-morbid psychiatric diseases were excluded by experienced psychiatrists.
Recruitment/selection of patients	Participants were recruited amongst patients seeking treatment at the Tinnitus Research Group of the Otolaryngology Department of the University of Sao Paulo School of Medicine.
Age, gender and ethnicity	Age - Other: over 18 years (average not reported). Gender (M:F): Not stated. Ethnicity: Not stated.
Further population details	1. Mild hearing loss: Not applicable 2. People with learning disability or cognitive impairment: Not applicable 3. Profoundly deaf: Not applicable

Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: Neuromodulation - Transcranial direct current stimulation (tDCS). At each session of 17 minutes, 1020 stimuli were administered with an intensity of 110% motor threshold at a frequency of 1 Hz over the left temporoparietal cortex. The resting motor threshold was determined at the beginning of the study as the minimal intensity that produced motor-evoked potentials of at least 5 microV in the right abductor digiti minimi muscle in five of 10 stimulations. The coil was centred at the midline between the electroencephalographic electrode positions T3 and P3 with the handle of the coil angled backward of about 45 degrees away from the midline TMS. . Duration 5 days (5 sessions). Concurrent medication/care: Not stated. Patients taking antidepressant, neuroleptic or anticonvulsant drugs were excluded.. Indirectness: No indirectness (n=9) Intervention 2: Control group - Sham/placebo intervention. Placebo stimulation was performed with a sham coil system which mimics the sound of active stimulation, without producing a magnetic field. All patients used ear plugs for hearing protection during both active and sham rTMS procedure. Duration 5 days (5 sessions). Concurrent medication/care: Not stated. Patients taking antidepressant, neuroleptic or anticonvulsant drugs were excluded.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS) versus SHAM/PLACEBO INTERVENTION

Protocol outcome 1: Tinnitus severity
- Actual outcome: Tinnitus Handicap Inventory at 1 month; Group 1: mean 19.4 (SD 17.6); n=10, Group 2: mean 28.9 (SD 25.9); n=9; Tinnitus Handicap Inventory 0-100 Top=High is poor outcome; Comments: Baselines, mean (SD):
tDCS group 29.8 (22.8)
Sham group 28.9 (23.8)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome: Tinnitus Handicap Inventory at 9 months ; Group 1: mean 22.8 (SD 18.2); n=10, Group 2: mean 29.6 (SD 23.5); n=9; Tinnitus Handicap Inventory 0-100 Top=High is poor outcome; Comments: Baselines, mean (SD):
tDCS group 29.8 (22.8)
Sham group 28.9 (23.8)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

- Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Tinnitus distress; Tinnitus annoyance; Health-related quality of life; Tinnitus-related quality of life; Tinnitus loudness; Depression; Anxiety; Anxiety and depression; Sleep; Adverse events: safety; Adverse events: tolerability/adherence/drop-outs/attrition; Adverse events: side effects (e.g. worsening of tinnitus)

Study	Pal 2015[35]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=42)
Countries and setting	Conducted in Switzerland; Setting: The study was conducted at the Centre Hospitalier Universitaire Vaudois (CHUV), University of Lausanne, 2012 to 2013.
Line of therapy	Unclear
Duration of study	Intervention + follow up: 5 days + 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients underwent a detailed neurological and ORL exam with audiological assessment and brain MRI.
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with chronic (>=1 year) non-pulsatile subjective tinnitus and age-adjusted normal hearing according to the Presbycusis Scale (progressive high frequency sensorineural hearing loss due to aging, measured by pure tone audiometry; <=5 dB below 10% of age/gender group in all frequencies and no conductive hearing loss >=15 dB) were included.
Exclusion criteria	Exclusion criteria were pulsatile tinnitus, secondary causes of tinnitus, concurrent tinnitus treatment, ear diseases, hearing impairment beyond presbycusis, acoustic trauma, vestibular disorders, prior exposure to tDCS, brain diseases or trauma, significant medical and/or psychiatric illnesses, cognitive impairment (<=24/30 on the Mini-Mental State Examination [MMSE]), pregnancy, epilepsy, substance abuse, and metal devices in the head.
Recruitment/selection of patients	Patients were recruited from the Clinic of Otolaryngology, but participation took place at the Clinic of Neurology.
Age, gender and ethnicity	Age - Mean (SD): tDCS group 51.6 (12.2) ; sham group 48 (9.9). Gender (M:F): 24 male / 18 female.

	Ethnicity: Not stated.
Further population details	1. Mild hearing loss: Not applicable 2. People with learning disability or cognitive impairment: Not applicable 3. Profoundly deaf: Not applicable
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=21) Intervention 1: Neuromodulation - Transcranial direct current stimulation (tDCS). Patients underwent five sessions of real or sham stimulation over the course of five days (1x session/day; Monday-Friday). All were naive to tDCS. Patients were seated comfortably and a cap was fitted to ensure consistency between sessions. Electrodes were positioned using the International 10-20 EEG system. For real tDCS, a large anode (75 cm2; current density 0.027 mA/cm2) was placed at F3-Fz-F4 for PFC stimulation, and two small cathodes (35.75 cm2 each) placed at T3 and T4, roughly corresponding to the left and right AC. Direct current was transmitted by saline-soaked surface sponges that came with the CE-certified battery-driven constant current stimulator (BrainSTIM Transcranial Stimulator, EMS Medical, Bologna, Italy) used for stimulation. During real tDCS sessions, 2 mAwere delivered for 20 min. Duration 5 days. Concurrent medication/care: None stated.. Indirectness: No indirectness (n=22) Intervention 2: Control group - Sham/placebo intervention. For sham stimulation a small anode and cathode were placed 1 cm apart over the forehead to mimic the position of F3-Fz-F4, and two inactive electrodes placed at T3 and T4. This is standard procedure for preventing electrical current from possibly passing through the brain. Sham sessions lasted 20 minutes but consisted of delivering 1 mA for 90 s in a ramp-like fashion to provide the transient and inconsistent tingling felt in tDCS. This procedure has proven valid for blinding in therapeutic trials. The stimulating apparatus was set up out of sight of patients and blinded investigators. Duration 5 days. Concurrent medication/care: None stated. Indirectness: No indirectness
Funding	Academic or government funding (Intramural funding was received from the Neurology Division of the Department of Clinical Neurosciences and the Clinic of Otolaryngology, Head Neck & Ear Surgery, Centre Hospitalier Universitaire Vaudois.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS) versus SHAM/PLACEBO INTERVENTION	

Protocol outcome 1: Tinnitus severity
- Actual outcome: Tinnitus handicap inventory (THI) at Post-treatment; Group 1: mean 40.6 (SD 18.1); n=21, Group 2: mean 43.7 (SD 16.3); n=21; Tinnitus handicap inventory 0-100 Top=High is poor outcome; Comments: Baselines, mean (SD):
Active tDCS group 46.7 (20)
Sham tDCS group 46.4 (18.2)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: Worsening of tinnitus after 1 session (but worsening remitted within 24h indicating it was unrelated to tDCS)
- Actual outcome: Tinnitus handicap inventory (THI) at 3 month follow-up; Group 1: mean 39.6 (SD 21.8); n=21, Group 2: mean 45 (SD 20); n=21; Tinnitus handicap inventory (THI) 0-100 Top=High is poor outcome; Comments: Baselines, mean (SD):
Active tDCS group 46.7 (20)
Sham tDCS group 46.4 (18.2)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: Worsening of tinnitus after 1 session (but worsening remitted within 24h indicating it was unrelated to tDCS)
- Actual outcome: Subjective Tinnitus Severity Scale (STSS) at Post-treatment; Group 1: mean 9.5 (SD 2.7); n=21, Group 2: mean 10 (SD 2); n=21; Subjective Tinnitus Severity Scale (STSS) 0-16 Top=High is poor outcome; Comments: Baselines, mean (SD):
Active tDCS 10.6 (2.6)
Sham tDCS 10.1 (1.7)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: Worsening of tinnitus after 1 session (but worsening remitted within 24h indicating it was unrelated to tDCS)
- Actual outcome: Subjective Tinnitus Severity Scale (STSS) at 3 month follow-up; Group 1: mean 9.7 (SD 2.6); n=21, Group 2: mean 10 (SD 2.6); n=21; Subjective Tinnitus Severity Scale (STSS) 0-16 Top=High is poor outcome; Comments: Baselines, mean (SD):
Active tDCS 10.6 (2.6)
Sham tDCS 10.1 (1.7)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: Worsening of tinnitus after 1 session (but worsening remitted within 24h indicating it was unrelated to tDCS)
- Actual outcome: Tinnitus intensity on VAS at Post-treatment; Group 1: mean 55.7 (SD 25.1); n=21, Group 2: mean 41 (SD 23.9); n=21; Visual analogue scale (VAS) 0-100 Top=High is poor outcome; Comments: Baselines, mean (SD):
Active tDCS 57.0 (20.3)
Sham tDCS 59.4 (19.8)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: Worsening of tinnitus after 1 session (but worsening remitted within 24h indicating it was unrelated to tDCS)
- Actual outcome: Tinnitus intensity on VAS at 3 month follow-up; Group 1: mean 53.9 (SD 19.8); n=21, Group 2: mean 53.1 (SD 23); n=21; Visual analogue scale (VAS) 0-100 Top=High is poor outcome; Comments: Baselines, mean (SD):

Active tDCS 57.0 (20.3)
Sham tDCS 59.4 (19.8)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: Worsening of tinnitus after 1 session (but worsening remitted within 24h indicating it was unrelated to tDCS)
- Actual outcome: Clinical Global Impression Scale (CGI) at Post-treatment; Group 1: mean 4 (SD 0.4); n=21, Group 2: mean 4 (SD 0.7); n=21; Clinical Global Impression (CGI) 0-7 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: Worsening of tinnitus after 1 session (but worsening remitted within 24h indicating it was unrelated to tDCS)
- Actual outcome: Clinical Global Impression Scale (CGI) at 3 month follow-up; Group 1: mean 4 (SD 0.7); n=21, Group 2: mean 4 (SD 0.9); n=21; Clinical Global Impression (CGI) 0-7 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: Worsening of tinnitus after 1 session (but worsening remitted within 24h indicating it was unrelated to tDCS)

Protocol outcome 2: Tinnitus distress
- Actual outcome: Tinnitus distress on VAS at Post-treatment; Group 1: mean 40.5 (SD 25.5); n=21, Group 2: mean 29.5 (SD 22.7); n=21; Visual analogue scale (VAS) 0-100 Top=High is poor outcome; Comments: Baselines, mean (SD):
Active tDCS 55.2 (25.8)
Sham tDCS 54.2 (25.4)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: Worsening of tinnitus after 1 session (but worsening remitted within 24h indicating it was unrelated to tDCS)
- Actual outcome: Tinnitus distress on VAS at 3 month follow-up; Group 1: mean 44.4 (SD 21.4); n=21, Group 2: mean 49.2 (SD 25.1); n=21; Visual analogue scale (VAS) 0-100 Top=High is poor outcome; Comments: Baselines, mean (SD):
Active tDCS 55.2 (25.8)
Sham tDCS 54.2 (25.4)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: Worsening of tinnitus after 1 session (but worsening remitted within 24h indicating it was unrelated to tDCS)

Protocol outcome 3: Anxiety and depression
- Actual outcome: Hospital Anxiety and Depression Scale (HAD) at 1 month follow-up; Group 1: mean 12.4 (SD 7.3); n=21, Group 2: mean 15.3 (SD 6.9); n=21; Hospital Anxiety and Depression Scale (HAD) 0-21 Top=High is poor outcome; Comments: Baselines, mean (SD):
Active tDCS 14.6 (7.6)
Sham tDCS 15.1 (6.3)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover -

Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: Worsening of tinnitus after 1 session (but worsening remitted within 24h indicating it was unrelated to tDCS)	
Protocol outcomes not reported by the study	Tinnitus annoyance; Health-related quality of life; Tinnitus-related quality of life; Tinnitus loudness; Depression; Anxiety; Sleep; Adverse events: safety; Adverse events: tolerability/adherence/drop-outs/attrition; Adverse events: side effects (e.g. worsening of tinnitus)

Study	Sahlsten 2017[42]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=42)
Countries and setting	Conducted in Finland; Setting:
Line of therapy	Unclear
Duration of study	Intervention + follow up: 2 weeks + 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients underwent complete audiological and otological investigations and a 3D-MRI.
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Chronic (6 months to 10 years), uni- or bilateral tinnitus in the age group of 18-65 years.
Exclusion criteria	Not stated.
Age, gender and ethnicity	Age - Mean (SD): rTMS group 48.9 (13.1) ; Sham group 51.5 (10.7). Gender (M:F): 27 male, 12 female. Ethnicity: Not stated.
Further population details	1. Mild hearing loss: Not stated / Unclear 2. People with learning disability or cognitive impairment: People without learning disability or cognitive impairment 3. Profoundly deaf: Not profoundly deaf
Extra comments	Mean duration of tinnitus (SD): 5.1 (2.5) years. All patients were right handed, apart from one left handed participant in the control group.
Indirectness of population	No indirectness

Interventions	(n=22) Intervention 1: Neuromodulation - Repetitive transcranial magnetic stimulation (rTMS) . The TMS equipment used was NBS System 4.0 (Nexstim Ltd, Helsinki, Finland). Patients received 10 treatment sessions over 2 weeks (five daily weekday sessions). Each session consisted of 4000 pulses at a continuous 1 Hz rate given to the left superior temporal gyrus (STG) at 100% of the RMT. Patients used ear plugs during the treatment. In the active group, all patients received 10 full sessions, except for one patient in whom one session was only 2800 pulses (due to late arrival). Duration 10 sessions (2 weeks). Concurrent medication/care: Not stated.. Indirectness: No indirectness (n=20) Intervention 2: Control group - Sham/placebo intervention. For placebo stimulation, a 15-cm plastic block was attached to the coil without the patient seeing it. The added distance effectively lowered the E-field to the cortex to negligible amounts of 1-4 V/m. Patients used ear plugs during the treatment.. Duration 10 sessions (2 weeks). Concurrent medication/care: Not stated. Indirectness: No indirectness
Funding	Academic or government funding (Study was supported by the Finnish Governmental Hospital grants (EVO), the Finnish Research Foundation of Ear Diseases, and State research funding from the Hospital District of Southwest Finland.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (RTMS) versus SHAM/PLACEBO INTERVENTION

Protocol outcome 1: Tinnitus severity
- Actual outcome: Tinnitus intensity on VAS at Post-treatment (2 weeks); Group 1: mean 35.5 (SD 25.28); n=19, Group 2: mean 50.6 (SD 23.26); n=20; Visual Analogue Scale 0-100 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Only statistically significant difference in baseline characteristics of both groups was a mean tinnitus loudness match in the left ear (p=0.03).; Group 1 Number missing: 3, Reason: Discontinuation due to unpleasantness and lack of time (2)
Did not receive treatment according to protocol (1); Group 2 Number missing: 0
- Actual outcome: Tinnitus intensity on VAS at 3 month follow-up; Group 1: mean 38.5 (SD 27.03); n=19, Group 2: mean 50.3 (SD 25.04); n=20; Visual Analogue Scale 0-100 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Only statistically significant difference in baseline characteristics of both groups was a mean tinnitus loudness match in the left ear (p=0.03).; Group 1 Number missing: 3, Reason: Discontinuation due to unpleasantness and lack of time (2)

Did not receive treatment according to protocol (1); Group 2 Number missing: 0

Protocol outcome 2: Tinnitus distress
- Actual outcome: Tinnitus distress on VAS at Post-treatment (2 weeks); Group 1: mean 34.9 (SD 24.41); n=19, Group 2: mean 43.2 (SD 21.91); n=20; Visual Analogue Scale 0-100 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Only statistically significant difference in baseline characteristics of both groups was a mean tinnitus loudness match in the left ear (p=0.03).; Group 1 Number missing: 3, Reason: Discontinuation due to unpleasantness and lack of time (2)
Did not receive treatment according to protocol (1); Group 2 Number missing: 0
- Actual outcome: Tinnitus distress on VAS at 3 month follow-up; Group 1: mean 39.3 (SD 26.59); n=19, Group 2: mean 48.5 (SD 24.6); n=20; Visual Analogue Scale 0-100 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Only statistically significant difference in baseline characteristics of both groups was a mean tinnitus loudness match in the left ear (p=0.03).; Group 1 Number missing: 3, Reason: Discontinuation due to unpleasantness and lack of time (2)
Did not receive treatment according to protocol (1); Group 2 Number missing: 0

Protocol outcome 3: Tinnitus annoyance
- Actual outcome: Tinnitus annoyance on VAS at Post-treatment (2 weeks); Group 1: mean 36.5 (SD 24.41); n=19, Group 2: mean 43.2 (SD 21.91); n=20; Visual Analogue Scale 0-100 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Only statistically significant difference in baseline characteristics of both groups was a mean tinnitus loudness match in the left ear (p=0.03).; Group 1 Number missing: 3, Reason: Discontinuation due to unpleasantness and lack of time (2)
Did not receive treatment according to protocol (1); Group 2 Number missing: 0
- Actual outcome: Tinnitus annoyance on VAS at 3 month follow-up; Group 1: mean 39.6 (SD 26.59); n=19, Group 2: mean 46.1 (SD 24.6); n=20; Visual Analogue Scale 0-100 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Only statistically significant difference in baseline characteristics of both groups was a mean tinnitus loudness match in the left ear (p=0.03).; Group 1 Number missing: 3, Reason: Discontinuation due to unpleasantness and lack of time (2)
Did not receive treatment according to protocol (1); Group 2 Number missing: 0

Protocol outcome 4: Adverse events: tolerability/adherence/drop-outs/attrition
- Actual outcome: Discontinuation due to unpleasantness of stimulation at Post-treatment (2 weeks); Group 1: 2/22, Group 2: 0/20; Comments: Discontinued intervention because both felt the stimulation unpleasant and had difficulties to arrange time for the study.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low,

Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Only statistically significant difference in baseline characteristics of both groups was a mean tinnitus loudness match in the left ear (p=0.03).; Group 1 Number missing: 3, Reason: Discontinuation due to unpleasantness and lack of time (2) Did not receive treatment according to protocol (1); Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Health-related quality of life; Tinnitus-related quality of life; Tinnitus loudness; Depression; Anxiety; Anxiety and depression; Sleep; Adverse events: safety; Adverse events: side effects (e.g. worsening of tinnitus)

Study	Shekhawat 2018[44]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=13)
Countries and setting	Conducted in New Zealand
Line of therapy	Unclear
Duration of study	Intervention time: 1 day
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Continuous chronic tinnitus for more than 2 years.
Exclusion criteria	Participants were excluded if they had any contraindications to undergoing HD-tDCS (personal or family history of seizures, metal or electronic implants, pregnancy, heart conditions, brain surgery and others) as screened by a neurologist.
Recruitment/selection of patients	Recruited through the University of Auckland Hearing and Tinnitus Clinic, and Centre for Brain Research participant databases.
Age, gender and ethnicity	Age - Mean (SD): 53.6. Gender (M:F): All male.. Ethnicity: Not stated.
Further population details	1. Mild hearing loss: People with hearing loss (There was a mild sensorineural hearing loss up to 8 kHz among all the participants. Hearing loss reached up to a severe degree at extended high frequencies (up to 16 kHz).). 2. People with learning disability or cognitive impairment: People without learning disability or cognitive impairment 3. Profoundly deaf: Not profoundly deaf

Indirectness of population	No indirectness
Interventions	(n=6) Intervention 1: Neuromodulation - Transcranial direct current stimulation (tDCS). HD-tDCS was applied for 20 minutes in accordance with the recommendations of international guidelines for tDCS. A NeuroConn DC stimulator was used for all procedures. A 4 x 1 HD-tDCS was placed on the scalp with the central electrode (anode) placed on the right dorsolateral prefrontal cortex. Stimulation location was determined using the international 10-20 system. The anode was placed at F4 and four adjoining cathodes were placed at F2, FC4, F6, and AF4. Real stimulation was 20 minutes long and included a 30 second fade in/out period. Duration 20 minutes. Concurrent medication/care: Not stated.. Indirectness: No indirectness (n=7) Intervention 2: Control group - Sham/placebo intervention. Sham stimulation included only the 30 second fade in/out and there was no stimulation in between the fade in and fade out periods. Duration 20 minutes. Concurrent medication/care: Not stated.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS) versus SHAM/PLACEBO INTERVENTION

Protocol outcome 1: Tinnitus annoyance
- Actual outcome: Change in annoyance on numeric rating scale at Post-treatment (20 minutes); Group 1: mean 4.56 (SD 27.31); n=6, Group 2: mean -11.54 (SD 45.59); n=7; Comments: Scale range unclear
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Tinnitus loudness
- Actual outcome: Change in loudness on numeric rating scale at Post-treatment (20 minutes); Group 1: mean 13.57 (SD 26.89); n=6, Group 2: mean -2.44 (SD 28.13); n=7; Comments: Scale range unclear
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	Tinnitus severity; Tinnitus distress; Health-related quality of life; Tinnitus-related quality of life; Depression; Anxiety; Anxiety and depression; Sleep; Adverse events; safety; Adverse events; tolerability/adherence/drop-

outs/attrition; Adverse events: side effects (e.g. worsening of tinnitus)

Study	Tass 2012[47]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=63)
Countries and setting	Conducted in Germany
Line of therapy	Unclear
Duration of study	Intervention + follow up: 12 weeks + 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients (≥18 years) with chronic (≥6 months), tonal (reliable and repeated location of the tinnitus tone by a sinusoidal matching tone), subjective tinnitus, not engaged in other tinnitus therapy and able to hear the stimulation tones and up to moderate hearing impairment (up to 50dB within the frequency band of the stimulation tones measured by an audiogram from 0.125 to 12 kHz).
Exclusion criteria	Exclusion criteria were: Morbus Meniere, auditory hallucinations, symptomatic hearing disorders, tinnitus due to temporomandibular joint disorders, brainstem diseases, psychiatric disorders and objective tinnitus.
Recruitment/selection of patients	99 patients with tinnitus were screened in 8 centres; 36 patients did not fulfill the inclusion criteria, mainly due to presence of atonal tinnitus or tinnitus duration less than 6 months.
Age, gender and ethnicity	Age - Mean (SD): G1 45.7 (10.8) ; G2 47.7 (5.6) ; G3 50.0 (14.7) ; G4 50.3 (11.8) ; G5(control) 57.6 (6.3) . Gender (M:F): % male: G1 72.7 ; G2 83.3 ; G3 50 ; G4 75% ; G5(control) 60. Ethnicity: Not stated.
Further population details	1. Mild hearing loss: People with hearing loss (Up to 50 dB). 2. People with learning disability or cognitive impairment: People without learning disability or cognitive impairment 3. Profoundly deaf: Not profoundly deaf

Indirectness of population	No indirectness: The tinnitus frequency ft (from 100–10.000 Hz) was assessed with a pure tone matching, where intensity and frequency of the matching tone were controlled by the patient.
Interventions	(n=58) Intervention 1: Neuromodulation - Acoustic neuromodulation therapy. Patients were stimulated for 12 weeks using a portable acoustic device and comfortable earphones (loudness controlled by patient) followed by an additional off-stimulation 4-week period to assess lasting effects of acoustic CR neuromodulation. There were 4 active treatment groups, G1,G2,G3,G4, which all received different tone frequencies of treatment and are pooled here. (Further details of frequencies in each group are included as graphs in the paper.) G1 to G3 all received stimulation for 4–6hours every day, applied either continuously or split into several sessions not shorter than 1 hour each to utilize cumulative effects. G4 received stimulation for 1 hour max every day. Stimulation signals were generated based on a specific formula reflecting the logarithmic tonotopic organization of the auditory cortex and on the matched tinnitus (frequency ft) with an equal number of tones placed below and above tinnitus frequency. Stimulation tones were equally loud and just super-threshold. 4 tones per cycle were played in random order with 3 stimulation cycles followed by 2 silent cycles. Duration 12 weeks. Concurrent medication/care: Not stated.. Indirectness: No indirectness (n=5) Intervention 2: Control group - Sham/placebo intervention. The control group, G5, was based on a modified tinnitus frequency. Stimulation tones in the placebo group were administered at a calculated frequency (fp =0.7071 ft/(2n), fp within 300 to 600 Hz) below the patient's tinnitus frequency (whereas in the active treatment groups, the stimulation tones were of a frequency immediately above and below the sufferer's tinnitus frequency. See Figure 1 in the paper for more details on placebo design. Duration 12 weeks. Concurrent medication/care: Not stated. Indirectness: No indirectness
Funding	Study funded by industry (Dr. Peter Tass and Dr. Christian Hauptmann have a contractual relationship with ANM Adaptive Neuromodulation GmbH, the sponsor of the clinical trial. Dr. Peter Tass and Dr. Hans-Joachim Freund are holding shares of ANM Adaptive Neuromodulation GmbH.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ACOUSTIC NEUROMODULATION THERAPY versus SHAM/PLACEBO INTERVENTION

Protocol outcome 1: Tinnitus severity
- Actual outcome: Tinnitus Questionnaire at Post-treatment (12 weeks); Group 1: mean -10.77 (SD 10.66); n=58, Group 2: mean -8.4 (SD 7.1); n=5
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: The active intervention group is a pooling of 4 different treatment groups (G1 n=22, G2 n=12, G3 n=12, G4 n=12) who received different frequencies of intervention and different intervention lengths.; Baseline details: G1-4 intervention pooled

mean: 42.25
G5 (control): 29.2; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome: Tinnitus Questionnaire at 4 week follow-up (16 weeks); Group 1: mean -11.78 (SD 12.62); n=58, Group 2: mean -9.2 (SD 10.5); n=5
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: The active intervention group is a pooling of 4 different treatment groups (G1 n=22, G2 n=12, G3 n=12, G4 n=12) who received different frequencies of intervention and different intervention lengths.; Baseline details: G1-4 intervention pooled mean: 42.25
G5 (control): 29.2; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Tinnitus annoyance
- Actual outcome: Tinnitus annoyance on VAS at Post-treatment (12 weeks); Group 1: mean -15.21 (SD 22.9); n=58, Group 2: mean -2 (SD 16.4); n=5
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: The active intervention group is a pooling of 4 different treatment groups (G1 n=22, G2 n=12, G3 n=12, G4 n=12) who received different frequencies of intervention and different intervention lengths.; Baseline details: G1-4 intervention pooled mean: 63.9
G5 (control): 38.0; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome: Tinnitus annoyance on VAS at 4 week follow-up (16 weeks); Group 1: mean -10.61 (SD 24.01); n=58, Group 2: mean 2 (SD 33.5); n=5
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: The active intervention group is a pooling of 4 different treatment groups (G1 n=22, G2 n=12, G3 n=12, G4 n=12) who received different frequencies of intervention and different intervention lengths.; Baseline details: G1-4 intervention pooled mean: 63.9
G5 (control): 38.0; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Tinnitus loudness
- Actual outcome: Tinnitus loudness on VAS at Post-treatment (12 weeks); Group 1: mean -12.01 (SD 21.76); n=58, Group 2: mean -9 (SD 18.8); n=5
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: The active intervention group is a pooling of 4 different treatment groups (G1 n=22, G2 n=12, G3 n=12, G4 n=12) who received different frequencies of intervention and different intervention lengths.; Baseline details: G1-4 intervention pooled mean: 65.35
G5 (control): 43.0; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome: Tinnitus loudness on VAS at 4 week follow-up (16 weeks); Group 1: mean -11.19 (SD 23.26); n=58, Group 2: mean -1 (SD 28.8); n=5
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: The active intervention group is a pooling of 4 different treatment groups (G1 n=22, G2 n=12, G3 n=12, G4 n=12) who received different frequencies of intervention and different intervention lengths.; Baseline details: G1-4 intervention pooled mean: 65.35
G5 (control): 43.0; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	Tinnitus distress; Health-related quality of life; Tinnitus-related quality of life; Depression; Anxiety; Anxiety and depression; Sleep; Adverse events: safety; Adverse events: tolerability/adherence/drop-outs/attrition; Adverse events: side effects (e.g. worsening of tinnitus)

Study	Tyler 2017[51]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)
Countries and setting	Conducted in USA
Line of therapy	Unclear
Duration of study	Not clear: 6 weeks + 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Key inclusion criteria included individuals with sensorineural tinnitus who (a) were 22 to 65 years-of-age (b) had primarily a tonal quality to their tinnitus (c) had either unilateral or bilateral tinnitus (d) had experienced tinnitus for at least one year in duration (e) had engaged in at least one tinnitus therapy program and found it unhelpful.
Exclusion criteria	Key exclusion criteria included (a) acute or intermittent tinnitus (b) Meniere's disease, retro-cochlear disease or evidence of active middle-ear disease (c) any active implanted device such as a pacemaker or other neurostimulator or any other investigational device or drug (d) Beck Depression Inventory (BDI) of 30 or greater (e) Any drug known to mimic, increase, or decrease release or removal of a diffuse neuromodulator, such as norepinephrine, dopamine, serotonin, benzodiazepines, acetylcholine, psychoactive medications or medication known to cause or increase tinnitus.
Age, gender and ethnicity	Age - Mean (SD): VNS group 55.9 (7.6), Control group 54.9 (9.1). Gender (M:F): 25 male, 5 female. Ethnicity: Not stated.
Further population details	1. Mild hearing loss: People with hearing loss (Some hearing loss was present in the population, but patients

	with excessive hearing loss were excluded.). 2. People with learning disability or cognitive impairment: People without learning disability or cognitive impairment 3. Profoundly deaf: Not profoundly deaf
Extra comments	Chronic sensorineural tinnitus.
Indirectness of population	No indirectness
Interventions	(n=16) Intervention 1: Neuromodulation - Vagal nerve stimulation (VNS). VNS device implantation was typically performed under general anaesthesia by an otolaryngologist, apart from one participant who received general anaesthetic at their request. Implantation was done before randomization to active VNS or inactive control groups. The implantation involved placement of the lead's stimulation electrodes on the left vagus nerve in the carotid sheath. The lead connector was then tunneled subcutaneously to a pocket created in the left ancillary or pectoral region where it was attached to the implantable pulse generator. The device consisted of an implantable pulse generator (Model 1000 Serenity), an implantable lead and electrode (Model 3000), and an external controller system. The external controller system included a laptop computer (Dell Inspiron) with high quality circumaural headphones (Sennheiser, HD280-PRO), running the Tinnitus Application Programming Software (TAPS Model 4000) and an external controller. The external controller (Model 2000, connected to the laptop via USB) communicated wirelessly with the IPG stimulator. The software enabled the audiologist to program the stimulation parameters (amplitude (mA), frequency (Hz), pulse width (μs), duration (ms), review captured participants' programming history, and check lead impedance and battery status. The software also captured participants' programming history. Participants started the therapy after approximately one week of recovery from surgery. Stimulation was delivered to the left vagus nerve since this is the most common practice in VNS for epilepsy and depression. However, since the upstream targets are bilateral, stimulation likely affects both sides of the cerebral hemispheres. Each VNS stimulation consisted of fifteen 0.8 mA, constant current, charge balanced pulses (100 μs pulse width, at 30 Hz). The duration of the VNS pulse train was 0.5 seconds. Each pulse train was delivered approximately every 30 seconds for 2.5 hours. In no instance were settings outside those used for VNS in epilepsy or depression (output currents were ≤3.5 mA, frequencies were ≤30 Hz, pulse widths were ≤1000 μs and duty cycles (ON time / OFF times) ≤50%. Duration Participants performed the treatment at home for approximately 2.5 hours/day, 7 days/week, for 6 weeks. Concurrent medication/care: Exclusion criteria ensured that participants were not taking any drug known to mimic, increase, or decrease release or removal of a diffuse neuromodulator, such as norepinephrine, dopamine, serotonin, benzodiazepines, acetylcholine, psychoactive medications or medication known to cause or increase tinnitus. In the paired VNS group, each 0.5 s VNS pulse was presented simultaneously with a 0.5 s tone every 30 s for 2.5 hrs. Therapy tones excluded one or more of the participant's tinnitus frequencies. The tones paired with

	VNS were at least ½ octave away from the most prominent tinnitus frequency for each individual participant. The frequencies ranged from 170 to 16000 Hz. The sounds were played at an intensity based on the participant's comfort level and adjusted for any hearing loss at different frequencies and intensities were limited to 80 dB SPL. Each of the tone frequencies was made to appear to arise from various 3D locations (programmed using a KEMAR head model) in order to avoid a bias of presenting a tone (paired with VNS) from a single spatial location. The frequency and intensity (dB SPL) of each tone were randomly selected each time a VNS pulse was delivered.. Indirectness: No indirectness (n=14) Intervention 2: Control group - Sham/placebo intervention. In the control (unpaired) group, VNS was not paired with tones (10 minutes of tones only, 5 minutes of silence and no VNS; 2 hours of VNS only; 5 minutes of silence and no VNS, and 10 minutes of tones only) during the 2.5-hour period.. Duration Participants performed the treatment at home for approximately 2.5 hours/day, 7 days/week, for 6 weeks.. Concurrent medication/care: Exclusion criteria ensured that participants were not taking any drug known to mimic, increase, or decrease release or removal of a diffuse neuromodulator, such as norepinephrine, dopamine, serotonin, benzodiazepines, acetylcholine, psychoactive medications or medication known to cause or increase tinnitus.. Indirectness: No indirectness
Funding	Academic or government funding (This work was supported by grants from the National Institute on Deafness and other Communication Disorders (U44 DC010084-05).)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VAGAL NERVE STIMULATION (VNS) versus SHAM/PLACEBO INTERVENTION

Protocol outcome 1: Tinnitus severity
- Actual outcome: Tinnitus Handicap Inventory at 6 weeks (end of treatment); Group 1: mean -17.7 (SD 19.52); n=16, Group 2: mean -7.3 (SD 37.53); n=14; Comments: SDs are calculated from published CI ranges (using RevMan calculator).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome: Tinnitus Handicap Questionnaire at 6 weeks (end of treatment); Group 1: mean -2.5 (SD 10.88); n=16, Group 2: mean -7.5 (SD 15.39); n=14; Comments: SDs are calculated from published CI ranges (using RevMan calculator).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome: Tinnitus Functional Index at 6 weeks (end of treatment); Group 1: mean -2.03 (SD 9.63); n=16, Group 2: mean -7.5 (SD 15.39); n=14; Comments: SDs are calculated from published CI ranges (using RevMan calculator).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Tinnitus loudness - Actual outcome: Tinnitus loudness on VAS at 6 weeks (end of treatment); Group 1: mean -6.69 (SD 12.35); n=16, Group 2: mean -8.5 (SD 26.27); n=14; Comments: SDs are calculated from published CI ranges (using RevMan calculator). Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Tinnitus distress; Tinnitus annoyance; Health-related quality of life; Tinnitus-related quality of life; Depression; Anxiety; Anxiety and depression; Sleep; Adverse events: safety; Adverse events: tolerability/adherence/drop-outs/attrition; Adverse events: side effects (e.g. worsening of tinnitus)

Study	Yilmaz 2014[58]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in Turkey
Line of therapy	Unclear
Duration of study	Intervention + follow up: 10 days + 1 month
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Examinations included a detailed history, detailed earn-nose-throat examination, complete blood cell count, extensive biochemical examinations and audiologic tests.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Normal ear-nose-throat examination, complaint of tinnitus lasting for at least 6 months and a hearing threshold below 30 dB in pure voice audiogram.
Exclusion criteria	Cases with a disease that may lead to objective tinnitus, cases with an anatomic problem or a disease relating to the external or middle ear, a history of ear operation, pacemaker, uncontrolled hypertension and diabetes, pregnant or breastfeeding individuals, cases with neuropsychiatric problems.
Recruitment/selection of patients	Patients applied to a polyclinic of Ear-Nose-Throat Department, Cerrahpasa Medical Faculty, Istanbul University.
Age, gender and ethnicity	Age - Mean (SD): 49.5 (8.03). Gender (M:F): Not reported.. Ethnicity: Not stated.
Further population details	1. Mild hearing loss: Not stated / Unclear 2. People with learning disability or cognitive impairment: People without learning disability or cognitive impairment 3. Profoundly deaf: Not profoundly deaf
Indirectness of population	No indirectness

Interventions	(n=30) Intervention 1: Neuromodulation - Repetitive transcranial magnetic stimulation (rTMS) . In TMS application, a Neuro-MS TMS device was used. The application was performed using a probe called a butterfly or an 8-shape coil for 30 minutes at low frequency (1 Hz). Duration 10 days (10 sessions). Concurrent medication/care: Not stated. Indirectness: No indirectness (n=30) Intervention 2: Control group - Sham/placebo intervention. Placebo. No details. Duration 10 days. Concurrent medication/care: Not stated. Indirectness: No indirectness
Funding	Other (Study states that no funding was received from the following organisations: National Institutes of Health, Wellcome Trust, Howard Hughes Medical Institute, and other(s).)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (RTMS) versus SHAM/PLACEBO INTERVENTION

Protocol outcome 1: Tinnitus severity
- Actual outcome: Tinnitus Handicap Index (THI) at 1 month follow-up; Group 1: mean 44.4 (SD 13.57); n=30, Group 2: mean 51.13 (SD 16.86); n=30; Tinnitus Handicap Index (THI) 0-100 Top=High is poor outcome; Comments: Baselines, mean (SD):
TMS group 52.76 (15.8)
Placebo group 51.46 (15.41)
Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Characteristics other than baseline values not reported.; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Tinnitus loudness
- Actual outcome: Tinnitus loudness on 0-10 rating scale at 1 month follow-up; Group 1: mean 50.093 (SD 13.6); n=30, Group 2: mean 50.609 (SD 13.35); n=30; Tinnitus on numeric rating scale 0-100 Top=High is poor outcome; Comments: Baselines, mean (SD):
TMS group 58.163 (14.81)
Placebo group 51.585 (12.67)
Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Characteristics other than baseline values not reported.; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	Tinnitus distress; Tinnitus annoyance; Health-related quality of life; Tinnitus-related quality of life; Depression;

Anxiety; Anxiety and depression; Sleep; Adverse events: safety; Adverse events: tolerability/adherence/drop-outs/attrition; Adverse events: side effects (e.g. worsening of tinnitus)	

Appendix E: Forest plots

E.1 rTMS (1 Hz) (low frequency) versus sham rTMS

Figure 2: Tinnitus severity (Tinnitus Handicap Inventory 0-100) (post-treatment)

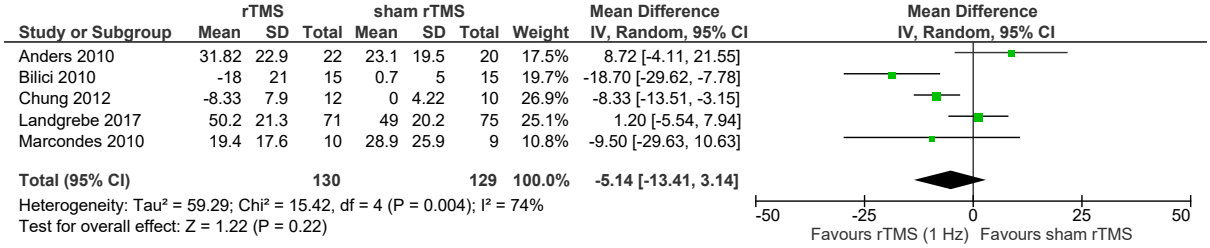


Figure 3: Tinnitus severity (Tinnitus Handicap Inventory 0-100) (1 month, 6 months, 26 weeks, 9 months follow-up)

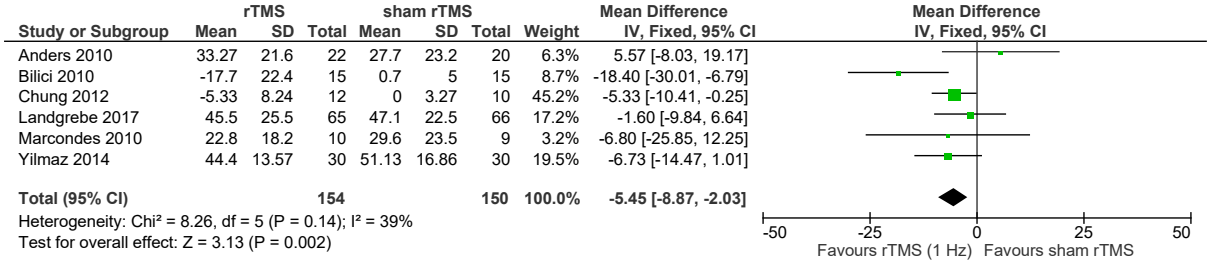


Figure 4: Tinnitus severity (Tinnitus Questionnaire 0-100) (post-treatment)

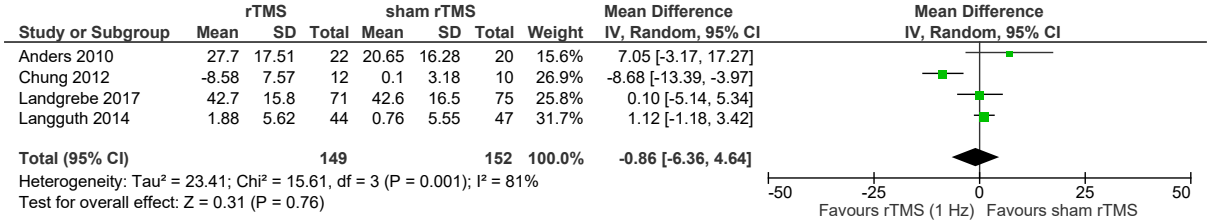


Figure 5: Tinnitus severity (Tinnitus Questionnaire 0-100) (1 month to 6 months follow-up)

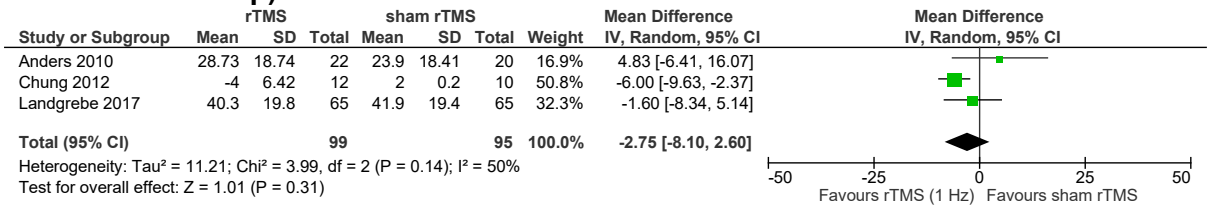


Figure 6: Tinnitus severity (Tinnitus Severity Index 0-100) (post-treatment)

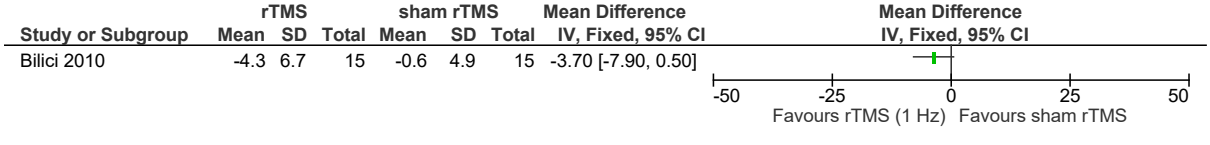


Figure 7: Tinnitus severity (Tinnitus Severity Index 0-100) (6 month follow-up)

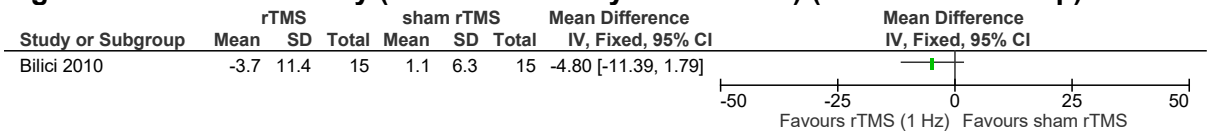


Figure 8: Tinnitus severity (Tinnitus Functional Index 0-100) (post-treatment)

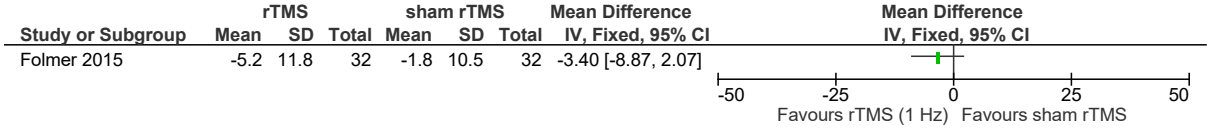


Figure 9: Tinnitus severity (Tinnitus Functional Index 0-100) (6 month follow-up)

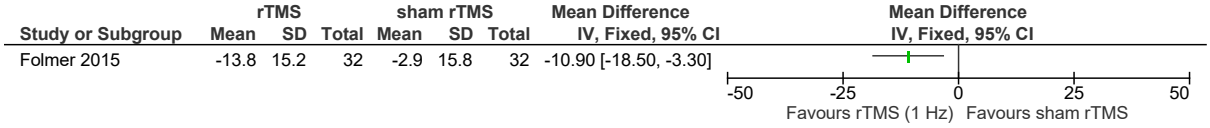


Figure 10: Tinnitus severity (tinnitus intensity on VAS 0-100) (post-treatment)

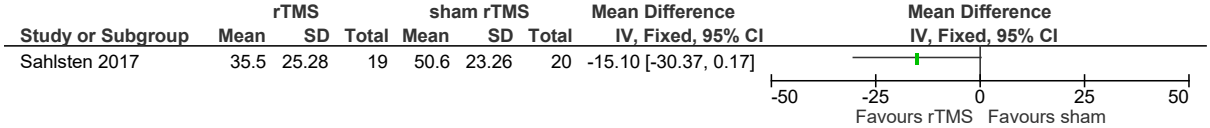


Figure 11: Tinnitus severity (tinnitus intensity on VAS 0-100) (3 month follow-up)

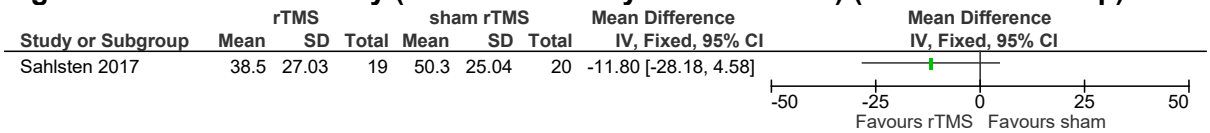


Figure 12: Health related quality of life (SF-12 Physical component 0-100) (post-treatment)

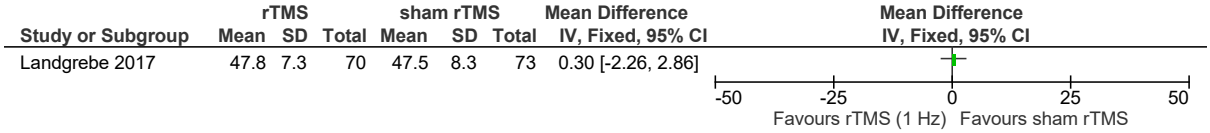


Figure 13: Health related quality of life (SF-12 Physical component 0-100) (6 month follow-up)

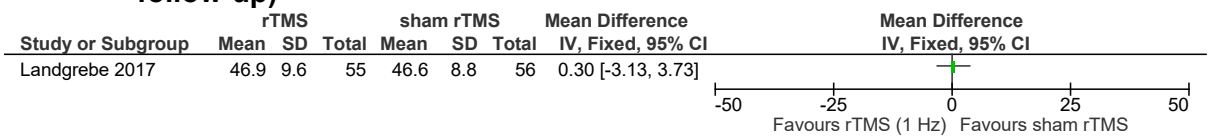


Figure 14: Health related quality of life (SF-12 Mental component 0-100) (post-treatment)

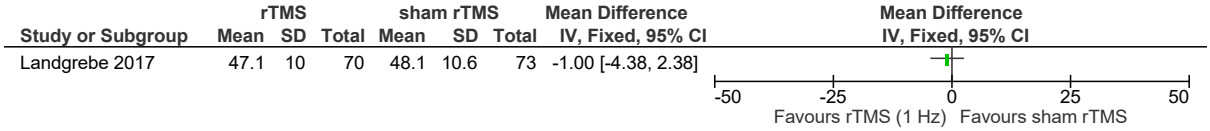


Figure 15: Health related quality of life (SF-12 Mental component 0-100) (6 month follow-up)

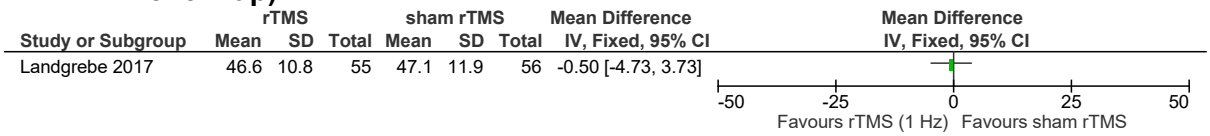


Figure 16: Tinnitus distress (VAS 0-100) (post-treatment)

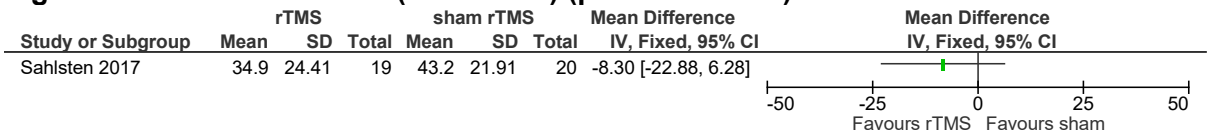


Figure 17: Tinnitus distress (VAS 0-100) (3 month follow-up)

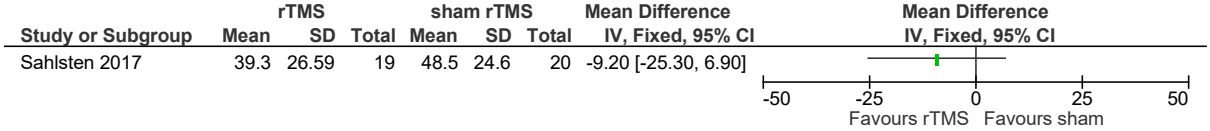


Figure 18: Tinnitus annoyance (VAS 0-100) (post-treatment)

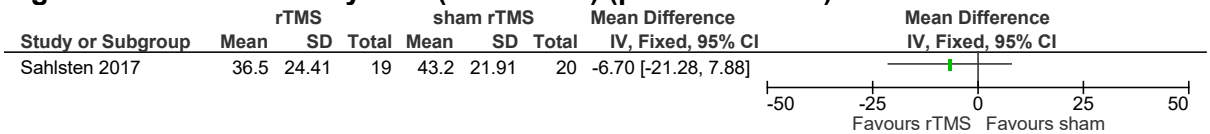


Figure 19: Tinnitus annoyance (VAS 0-100) (3 month follow-up)

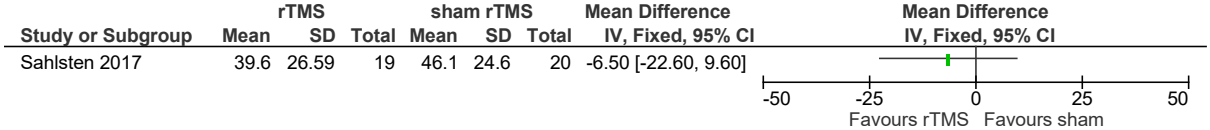


Figure 20: Anxiety (Beck Anxiety Inventory 0-63) (post-treatment)

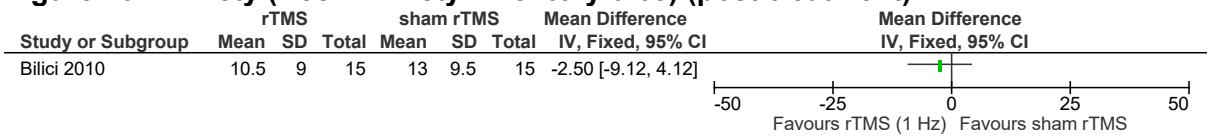


Figure 21: Anxiety (Beck Anxiety Inventory 0-63) (6 month follow-up)

Study or Subgroup	rTMS Mean	rTMS SD	rTMS Total	sham rTMS Mean	sham rTMS SD	sham rTMS Total	Mean Difference IV, Fixed, 95% CI
Bilici 2010	10.3	8.3	15	14.1	10.2	15	-3.80 [-10.45, 2.85]

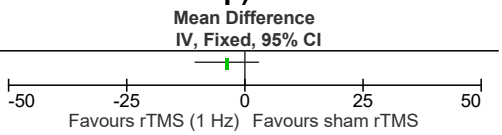


Figure 22: Depression (Beck Depression Inventory 0-63) (post-treatment)

Study or Subgroup	rTMS Mean	rTMS SD	rTMS Total	sham rTMS Mean	sham rTMS SD	sham rTMS Total	Mean Difference IV, Fixed, 95% CI
Landgrebe 2017	8.1	6.6	71	7.7	5.9	75	0.40 [-1.63, 2.43]

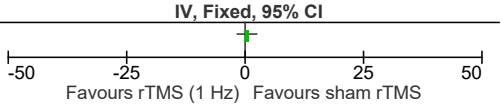


Figure 23: Depression (Beck Depression Inventory 0-63) (6 month follow-up)

Study or Subgroup	rTMS Mean	rTMS SD	rTMS Total	sham rTMS Mean	sham rTMS SD	sham rTMS Total	Mean Difference IV, Fixed, 95% CI
Landgrebe 2017	8.8	9.1	65	8.2	6.8	66	0.60 [-2.15, 3.35]

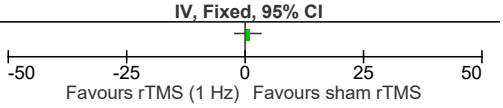


Figure 24: Tinnitus loudness (on 0-100 rating scale) (1 month follow-up)

Study or Subgroup	rTMS Mean	rTMS SD	rTMS Total	sham rTMS Mean	sham rTMS SD	sham rTMS Total	Mean Difference IV, Fixed, 95% CI
Yilmaz 2014	50.09	13.6	30	50.61	13.35	30	-0.52 [-7.34, 6.30]

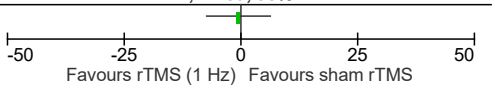
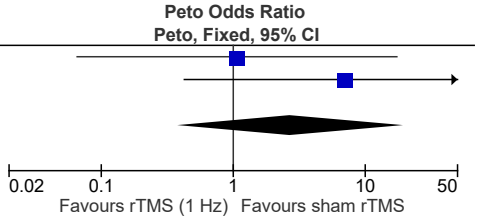


Figure 25: Drop out due to adverse events

Study or Subgroup	rTMS Events	rTMS Total	sham rTMS Events	sham rTMS Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Langguth 2014	1	45	1	48	50.4%	1.07 [0.07, 17.35]
Sahlsten 2017	2	22	0	20	49.6%	7.08 [0.43, 117.48]
Total (95% CI)		**67**		**68**	**100.0%**	**2.73 [0.38, 19.75]**
Total events	3		1			

Heterogeneity: Chi² = 0.88, df = 1 (P = 0.35); I² = 0%
Test for overall effect: Z = 0.99 (P = 0.32)



E.2 rTMS (10 Hz) (high frequency) versus sham rTMS

Figure 26: Tinnitus severity (Tinnitus Handicap Inventory 0-100) (post-treatment)

Study or Subgroup	rTMS (10 Hz) Mean	rTMS (10 Hz) SD	rTMS (10 Hz) Total	sham rTMS Mean	sham rTMS SD	sham rTMS Total	Mean Difference IV, Fixed, 95% CI
Bilici 2010	-9.7	8.8	15	0.7	5	15	-10.40 [-15.52, -5.28]

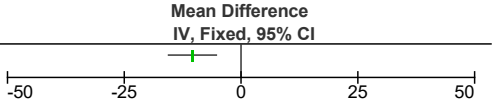


Figure 27: Tinnitus severity (Tinnitus Handicap Inventory 0-100) (6 month follow-up)

Study or Subgroup	rTMS (10 Hz) Mean	rTMS (10 Hz) SD	rTMS (10 Hz) Total	sham rTMS Mean	sham rTMS SD	sham rTMS Total	Mean Difference IV, Fixed, 95% CI
Bilici 2010	-15.2	11.7	15	0.7	5	15	-15.90 [-22.34, -9.46]

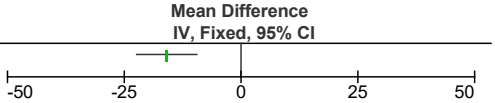


Figure 248: Tinnitus severity (Tinnitus Severity Index 0-100) (post-treatment)

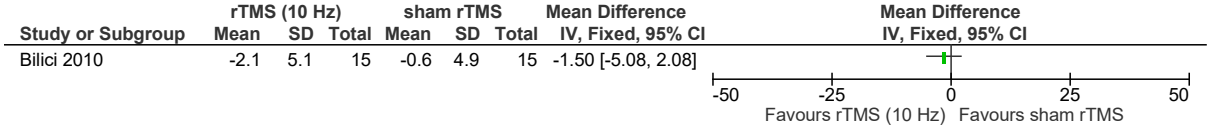


Figure 29: Tinnitus severity (Tinnitus Severity Index 0-100) (6 month follow-up)

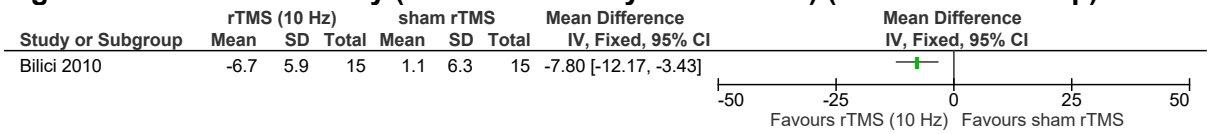


Figure 30: Anxiety (Beck Anxiety Inventory 0-63) (post-treatment)

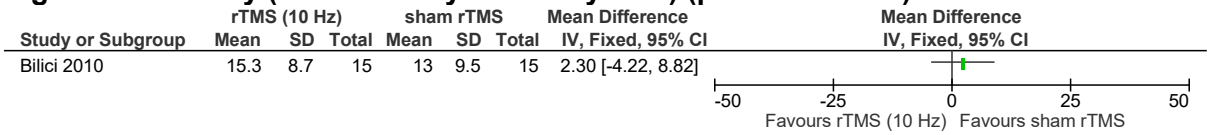
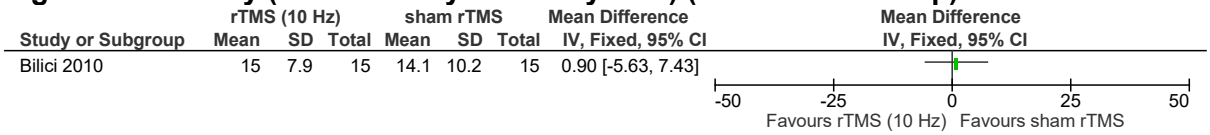
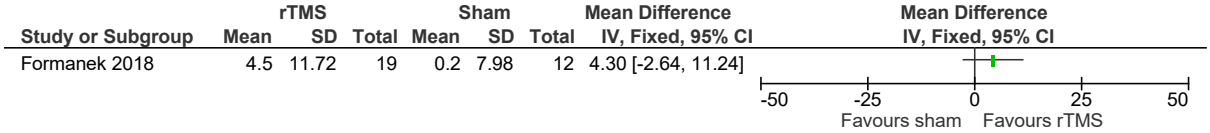


Figure 31: Anxiety (Beck Anxiety Inventory 0-63) (6 month follow-up)



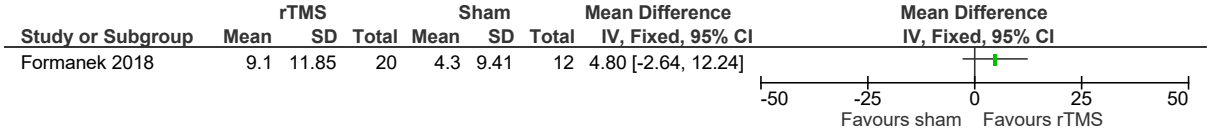
E.3 rTMS (1 Hz + 25 Hz) (combined frequency) versus sham rTMS

Figure 32: Tinnitus severity (Tinnitus Handicap Inventory, change score) (1 month follow-up)



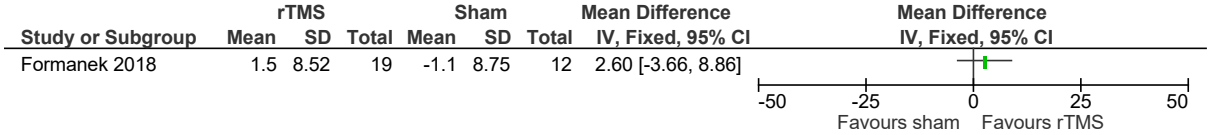
Note: Higher value means tinnitus improvement.

Figure 33: Tinnitus severity (Tinnitus Handicap Inventory, change score) (6 month follow-up)



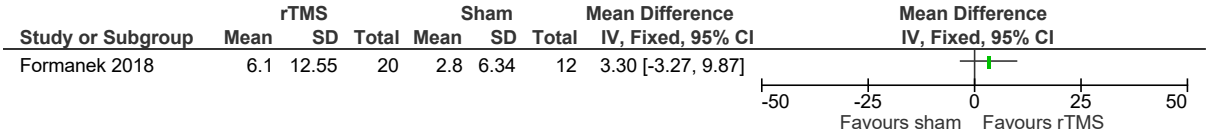
Note: Higher value means tinnitus improvement.

Figure 34: Tinnitus severity (Tinnitus Handicap Questionnaire, change score) (1 month follow-up)



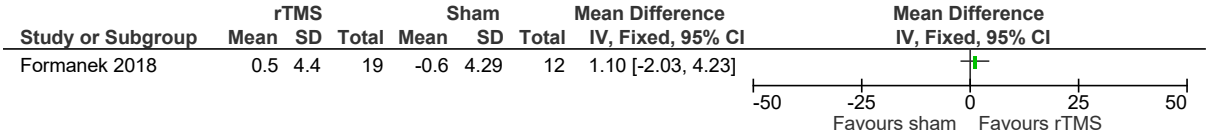
Note: Higher value means tinnitus improvement.

Figure 35: Tinnitus severity (Tinnitus Handicap Questionnaire, change score) (6 month follow-up)



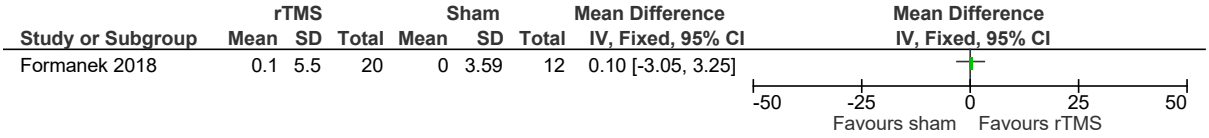
Note: Higher value means tinnitus improvement.

Figure 36: Depression (Beck Depression Inventory, change score) (1 month follow-up)



Note: Higher value means tinnitus improvement.

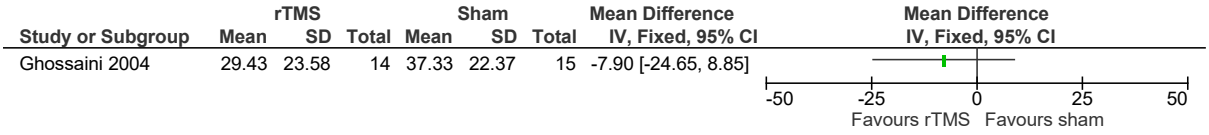
Figure 37: Depression (Beck Depression Inventory, change score) (6 month follow-up)



Note: Higher value means tinnitus improvement.

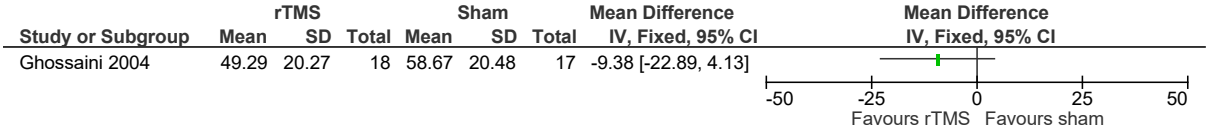
E.4 rTMS (27 MHz) (very high frequency) versus sham rTMS

Figure 38: Tinnitus severity (Tinnitus Handicap Inventory 0-100) (post-treatment)



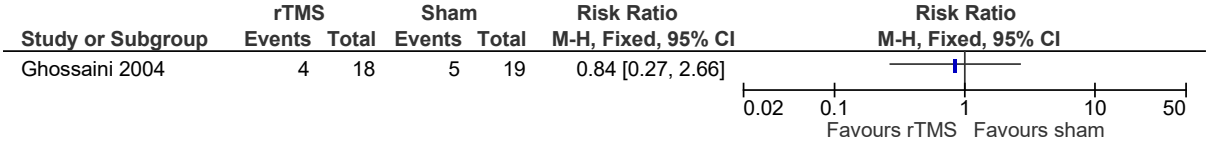
Note: Difference in outcome at baseline. Baselines, mean (SD): rTMS group 33.78 (22.15), sham group 39.30 (22.55)

Figure 39: Tinnitus severity (Tinnitus Magnitude Rating, 0-100 numeric rating scale) (post-treatment)



Note: Difference in outcome at baseline. Baselines, mean (SD): rTMS group 51.11 (21.04), sham group 59.38 (17.5)

Figure 40: Patient-reported subjective worsening of tinnitus (post-treatment)



E.5 Right dorsolateral prefrontal cortex (DLPFC) tDCS versus sham tDCS

Figure 41: Tinnitus severity (Tinnitus Handicap Inventory 0-100) (post-treatment)

	rTMS (1 Hz)			sham rTMS			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Pal 2015	40.6	18.1	21	43.7	16.3	21	-3.10 [-13.52, 7.32]	

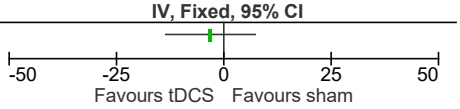


Figure 42: Tinnitus severity (Tinnitus Handicap Inventory 0-100) (3 month follow-up)

	Experimental			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Pal 2015	39.6	21.8	21	45	20	21	-5.40 [-18.05, 7.25]	

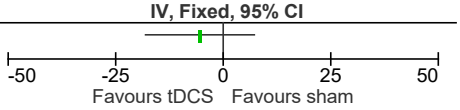


Figure 43: Tinnitus severity (Subjective Tinnitus Severity Scale 0-16) (post-treatment)

	Experimental			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Pal 2015	9.5	2.7	21	10	2	21	-0.50 [-1.94, 0.94]	

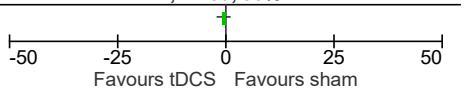


Figure 44: Tinnitus severity (Subjective Tinnitus Severity Scale 0-16) (3 month follow-up)

	Experimental			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Pal 2015	9.7	2.6	21	10	2.6	21	-0.30 [-1.87, 1.27]	

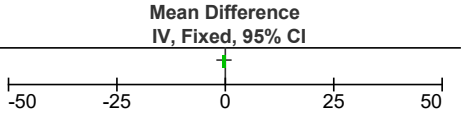


Figure 45: Tinnitus severity (tinnitus intensity on VAS 0-100) (post-treatment)

	Experimental			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Pal 2015	55.7	25.1	21	41	23.9	21	14.70 [-0.12, 29.52]	

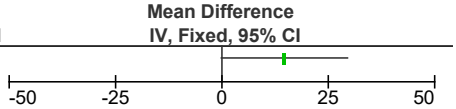


Figure 46: Tinnitus severity (tinnitus intensity on VAS 0-100) (3 month follow-up)

	Experimental			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Pal 2015	53.9	19.8	21	53.1	23	21	0.80 [-12.18, 13.78]	

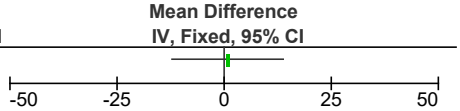


Figure 47: Tinnitus severity (Clinical Global Impression Scale 0-7) (post-treatment)

	Experimental			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Pal 2015	4	0.4	21	4	0.7	21	0.00 [-0.34, 0.34]	

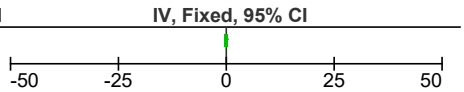


Figure 48: Tinnitus severity (Clinical Global Impression Scale 0-7) (3 month follow-up)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Pal 2015	4	0.7	21	4	0.9	21	0.00 [-0.49, 0.49]

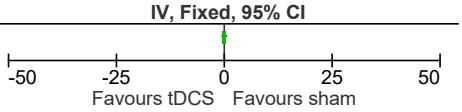


Figure 49: Tinnitus distress (VAS 0-100) (post-treatment)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Pal 2015	40.5	25.5	21	29.5	22.7	21	11.00 [-3.60, 25.60]

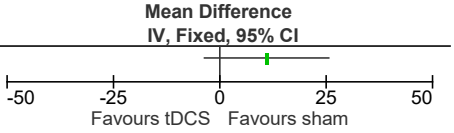


Figure 50: Tinnitus distress (VAS 0-100) (3 month follow-up)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Pal 2015	44.4	21.4	21	49.2	25.1	21	-4.80 [-18.91, 9.31]

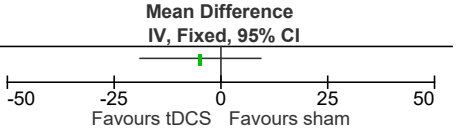


Figure 51: Tinnitus annoyance (numeric rating scale 0-100) (post-treatment)

Study or Subgroup	tDCS Mean	SD	Total	sham tDCS Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Shekhawat 2018	4.56	27.31	6	-11.54	45.59	7	16.10 [-24.13, 56.33]

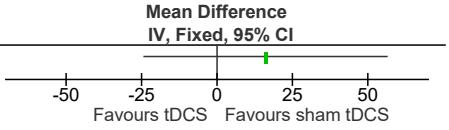


Figure 52: Tinnitus loudness (numeric rating scale 0-100) (post-treatment)

Study or Subgroup	tDCS Mean	SD	Total	sham tDCS Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Shekhawat 2018	13.57	26.89	6	-2.44	28.13	7	16.01 [-13.94, 45.96]

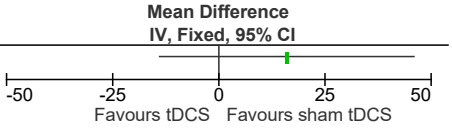
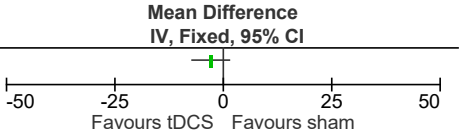


Figure 53: Anxiety and depression (Hospital Anxiety and Depression Scale 0-21) (1 month follow-up)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Pal 2015	12.4	7.3	21	15.3	6.9	21	-2.90 [-7.20, 1.40]



E.6 Left temporal area (LTA) tDCS versus sham tDCS

Figure 54: Tinnitus severity (Tinnitus Handicap Inventory 0-100) (post-treatment)

Study or Subgroup	rTMS (1 Hz) Mean	SD	Total	sham rTMS Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Forogh 2016	58.6	28.1	10	54.1	24.9	10	4.50 [-18.77, 27.77]

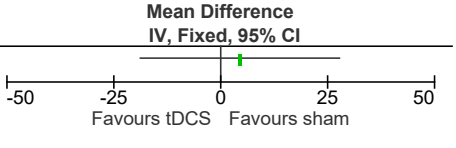


Figure 55: Tinnitus severity (Tinnitus Handicap Inventory 0-100) (2 weeks follow-up)

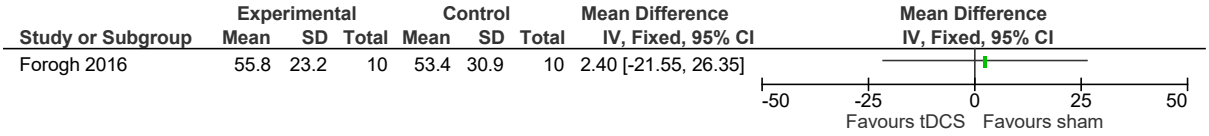


Figure 56: Tinnitus distress (VAS 0-10) (post-treatment)

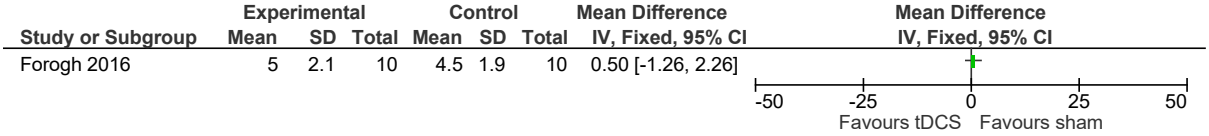


Figure 57: Tinnitus distress (VAS 0-10) (2 week follow-up)

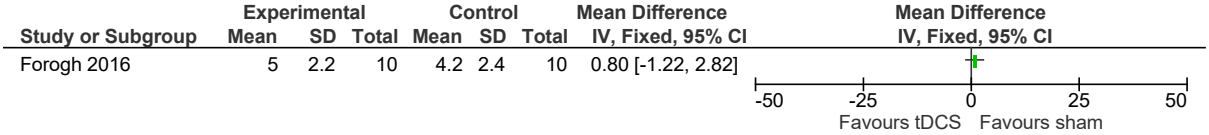


Figure 58: Tinnitus loudness (VAS 0-10) (post-treatment)

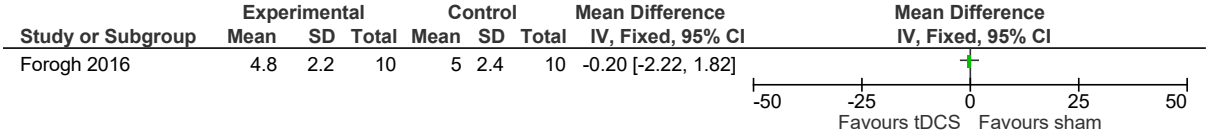
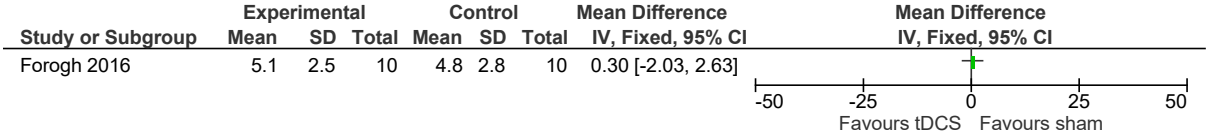


Figure 59: Tinnitus loudness (VAS 0-10) (2 weeks follow-up)



E.7 VNS versus sham VNS

Figure 60: Tinnitus severity (Tinnitus Handicap Inventory 0-100) (post-treatment)

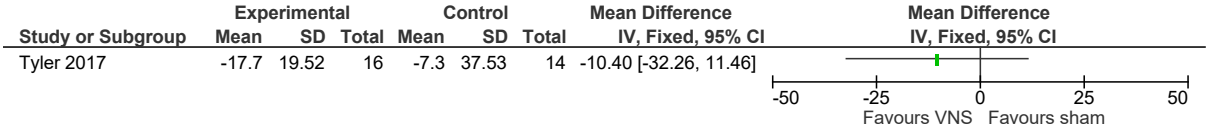


Figure 61: Tinnitus severity (Tinnitus Handicap Questionnaire 0-100) (post-treatment)

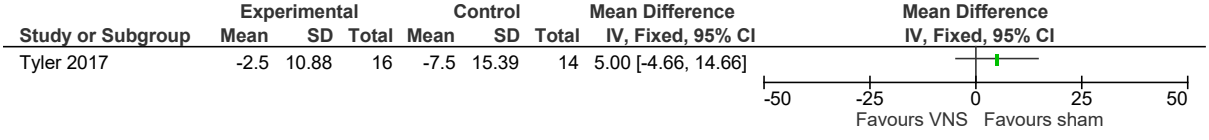


Figure 62: Tinnitus severity (Tinnitus Functional Index 0-100) (post-treatment)

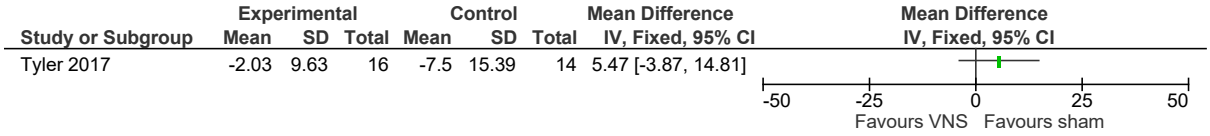
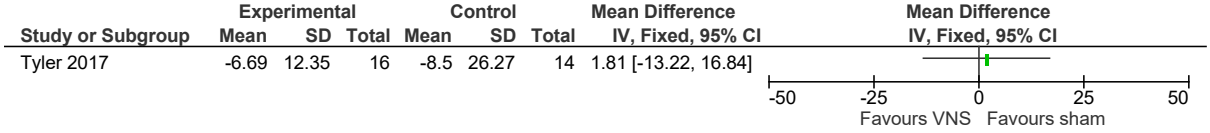


Figure 63: Tinnitus loudness (VAS 0-100) (post-treatment)



E.8 Acoustic CR versus placebo/sham

Figure 64: Tinnitus severity (Tinnitus Questionnaire 0-100) (post-treatment)

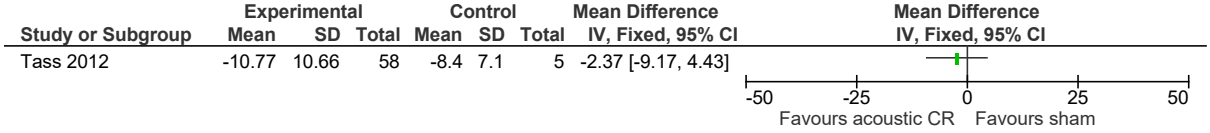


Figure 65: Tinnitus severity (Tinnitus Questionnaire 0-100) (4 week follow-up)

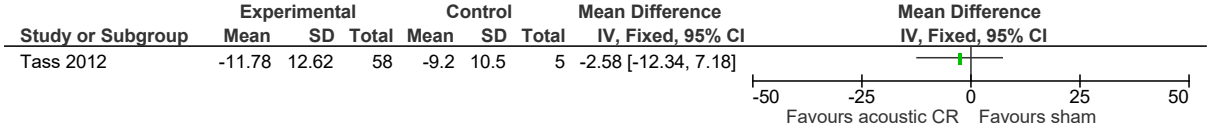


Figure 66: Tinnitus annoyance (VAS 0-100) (post-treatment)

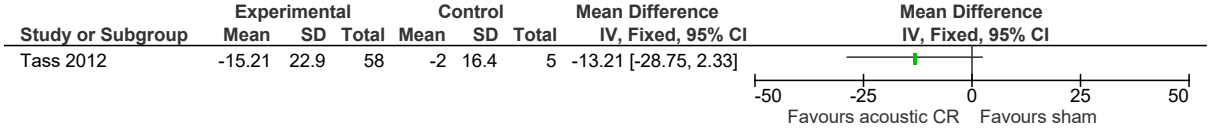


Figure 67: Tinnitus annoyance (VAS 0-100) (4 week follow-up)

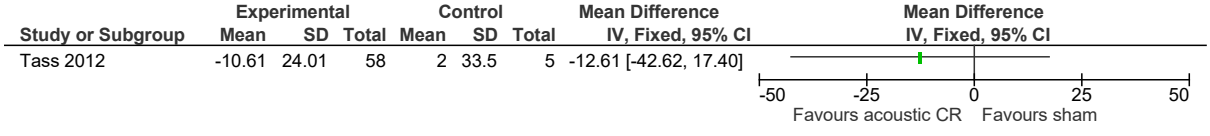


Figure 68: Tinnitus loudness (VAS 0-100) (post-treatment)

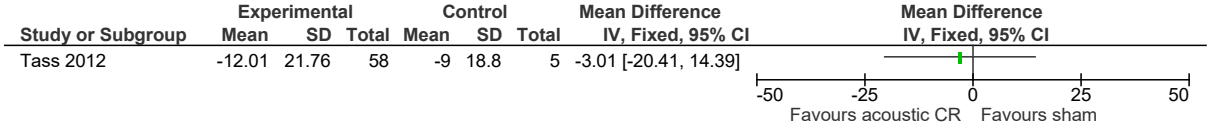
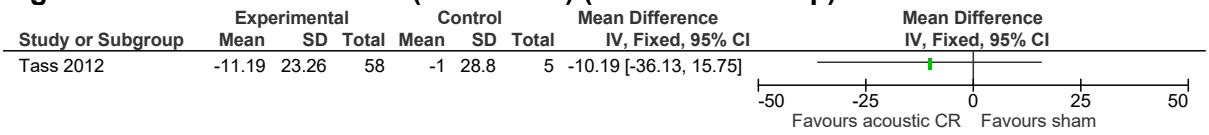


Figure 69: Tinnitus loudness (VAS 0-100) (4 week follow-up)



Appendix F: GRADE tables

Table 15: Clinical evidence profile: rTMS (1 Hz) (low frequency) versus sham rTMS for tinnitus

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RTMS (1 Hz) (low frequency)	Sham rTMS	Relative (95% CI)	Absolute		
Tinnitus severity (Tinnitus Handicap Inventory) (post-treatment) (range of scores: 0-100; Better indicated by lower values)												
5	randomised trials	very serious[1]	serious[2]	no serious indirectness	serious[3]	none	130	129	-	MD 5.14 lower (13.41 to 3.14 higher)	⊕OOO VERY LOW	CRITICAL
Tinnitus severity (Tinnitus Handicap Inventory) (1 month to 9 months follow-up) (range of scores: 0-100; Better indicated by lower values)												
6	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	154	150	-	MD 5.45 lower (8.87 to 2.03 lower)	⊕⊕OO LOW	CRITICAL
Tinnitus severity (Tinnitus Questionnaire) (post-treatment) (range of scores: 0-100; Better indicated by lower values)												
4	randomised trials	very serious[1]	very serious[2]	no serious indirectness	serious[3]	none	149	152	-	MD 0.86 lower (6.36 lower to 4.64 higher)	⊕OOO VERY LOW	CRITICAL
Tinnitus severity (Tinnitus Questionnaire) (1 month to 6 months follow-up) (range of scores: 0-100; Better indicated by lower values)												
3	randomised trials	very serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	99	95	-	MD 2.75 lower (8.1 lower to 2.6 higher)	⊕OOO VERY LOW	CRITICAL
Tinnitus severity (Tinnitus Severity Index) (post-treatment) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	15	15	-	MD 3.7 lower (7.9 lower to 0.5 higher)	⊕OOO VERY LOW	CRITICAL
Tinnitus severity (Tinnitus Severity Index) (6 month follow-up) (range of scores: 0-100; Better indicated by lower values)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	15	15	-	MD 4.8 lower (11.39 lower to 1.79 higher)	⊕OOO VERY LOW	CRITICAL
Tinnitus severity (Tinnitus Functional Index) (post-treatment) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	32	32	-	MD 3.4 lower (8.87 lower to 2.07 higher)	⊕⊕⊕O MODERATE	CRITICAL
Tinnitus severity (Tinnitus Functional Index) (6 month follow-up) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	32	32	-	MD 10.9 lower (18.5 to 3.3 lower)	⊕⊕⊕O MODERATE	CRITICAL
Tinnitus severity (tinnitus intensity on VAS) (post-treatment) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	19	20	-	MD 15.1 lower (30.37 lower to 0.17 higher)	⊕OOO VERY LOW	CRITICAL
Tinnitus severity (tinnitus intensity on VAS) (3 month follow-up) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	19	20	-	MD 11.8 lower (28.18 lower to 4.58 higher)	⊕OOO VERY LOW	CRITICAL
Health related quality of life (SF-12 Physical component) (post-treatment) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	70	73	-	MD 0.3 higher (2.26 lower to 2.86 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Health related quality of life (SF-12 Physical component) (6 month follow-up) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	55	56	-	MD 0.3 higher (3.13 lower to 3.73 higher)	⊕⊕OO LOW	CRITICAL
Health related quality of life (SF-12 Mental component) (post-treatment) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	70	73	-	MD 1 lower (4.38 lower to 2.38 higher)	⊕⊕⊕⊕ HIGH	CRITICAL

Health related quality of life (SF-12 Mental component) (6 month follow-up) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	55	56	-	MD 0.5 lower (4.73 lower to 3.73 higher)	⊕⊕OO LOW	CRITICAL
Tinnitus distress (VAS) (post-treatment) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	19	20	-	MD 8.3 lower (22.88 lower to 6.28 higher)	⊕OOO VERY LOW	CRITICAL
Tinnitus distress (VAS) (3 month follow-up) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	19	20	-	MD 9.2 lower (25.3 lower to 6.9 higher)	⊕OOO VERY LOW	CRITICAL
Tinnitus annoyance (VAS) (post-treatment) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	19	20	-	MD 6.7 lower (21.28 lower to 7.88 higher)	⊕OOO VERY LOW	CRITICAL
Tinnitus annoyance (VAS) (3 month follow-up) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	19	20	-	MD 6.5 lower (22.6 lower to 9.6 higher)	⊕OOO VERY LOW	CRITICAL
Anxiety (Beck Anxiety Inventory) (post-treatment) (range of scores: 0-63; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	15	15	-	MD 2.5 lower (9.12 lower to 4.12 higher)	⊕OOO VERY LOW	IMPORTANT
Anxiety (Beck Anxiety Inventory) (6 month follow-up) (range of scores: 0-63; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	15	15	-	MD 3.8 lower (10.45 lower to 2.85 higher)	⊕OOO VERY LOW	IMPORTANT
Depression (Beck Depression Inventory) (post-treatment) (range of scores: 0-63; Better indicated by lower values)												
1	randomised	no serious	no serious	no serious	no serious	none	71	75	-	MD 0.4 higher (1.63	⊕⊕⊕⊕	IMPORTANT

	trials	risk of bias	inconsistency	indirectness	imprecision					lower to 2.43 higher)	HIGH	
Depression (Beck Depression Inventory) (6 month follow-up) (range of scores: 0-63; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	71	75	-	MD 0.6 higher (2.15 lower to 3.35 higher)	⊕⊕OO LOW	IMPORTANT
Tinnitus loudness (1 month follow-up) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	30	30	-	MD 0.52 lower (7.34 lower to 6.3 higher)	⊕OOO VERY LOW	IMPORTANT
Drop out due to adverse events												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	3/67 (4.5%)	1/68 (1.5%)	OR 2.73 (0.38 to 19.75)	24 more per 1000 (from 9 fewer to 213 more)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Heterogeneity, I2=50%, p=0.04, unexplained by subgroup analysis.
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 16: Clinical evidence profile: rTMS (10 Hz) (high frequency) versus sham rTMS for tinnitus

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**RTMS (10 Hz) (high frequency)**	**Sham rTMS**	**Relative (95% CI)**	**Absolute**		
Tinnitus severity (Tinnitus Handicap Inventory) (post-treatment) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	15	15	-	MD 10.4 lower (15.52 to 5.28 lower)	⊕⊕OO LOW	CRITICAL
Tinnitus severity (Tinnitus Handicap Inventory) (6 month follow-up) (range of scores: 0-100; Better indicated by lower values)												
1	randomised	very	no serious	no serious	no serious	none	15	15	-	MD 15.9 lower (22.34	⊕⊕OO	CRITICAL

	trials	serious[1]	inconsistency	indirectness	imprecision					to 9.46 lower)	LOW	
Tinnitus severity (Tinnitus Severity Index) (post-treatment) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15	15	-	MD 1.5 lower (5.08 lower to 2.08 higher)	⊕OOO VERY LOW	CRITICAL
Tinnitus severity (Tinnitus Severity Index) (6 month follow-up) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	15	15	-	MD 7.8 lower (12.17 to 3.43 lower)	⊕⊕OO LOW	CRITICAL
Anxiety (Beck Anxiety Inventory) (post-treatment) (range of scores: 0-63; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15	15	-	MD 2.3 higher (4.22 lower to 8.82 higher)	⊕OOO VERY LOW	IMPORTANT
Anxiety (Beck Anxiety Inventory) (6 month follow-up) (range of scores: 0-63; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	15	15	-	MD 0.9 higher (5.63 lower to 7.43 higher)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 17: Clinical evidence profile: rTMS (1 Hz + 25 Hz) (combined frequency) versus sham rTMS for tinnitus

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**RTMS (1 Hz + 25 Hz) (combined frequency)**	**Sham rTMS**	**Relative (95% CI)**	**Absolute**		
Tinnitus severity (Tinnitus Handicap Inventory, change score) (1 month follow-up) (follow-up 1 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	19	12	-	MD 4.3 higher (2.64 lower to 11.24 higher)	⊕⊕OO LOW	CRITICAL

Tinnitus severity (Tinnitus Handicap Inventory, change score) (6 month follow-up) (follow-up 6 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20	12	-	MD 4.8 higher (2.64 lower to 12.24 higher)	⊕⊕OO LOW	CRITICAL
Tinnitus severity (Tinnitus Handicap Questionnaire, change score) (1 month follow-up) (follow-up 1 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	19	12	-	MD 2.6 higher (3.66 lower to 8.86 higher)	⊕⊕OO LOW	CRITICAL
Tinnitus severity (Tinnitus Handicap Questionnaire, change score) (6 month follow-up) (follow-up 6 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20	12	-	MD 3.3 higher (3.27 lower to 9.87 higher)	⊕⊕OO LOW	CRITICAL
Depression (Beck Depression Inventory, change score) (1 month follow-up) (follow-up 1 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	19	12	-	MD 1.1 higher (2.03 lower to 4.23 higher)	⊕⊕OO LOW	IMPORTANT
Depression (Beck Depression Inventory, change score) (6 month follow-up) (follow-up 6 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	20	12	-	MD 0.1 higher (3.05 lower to 3.25 higher)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 18: Clinical evidence profile: rTMS (27 MHz) (very high frequency) versus sham rTMS for tinnitus

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**RTMS (27 MHz) (very high frequency)**	**Sham rTMS**	**Relative (95% CI)**	**Absolute**		
Tinnitus severity (Tinnitus Handicap Inventory 0-100) (post-treatment) (follow-up 2 weeks; range of scores: 0-100; Better indicated by lower values)												
1	randomised	very	no serious	no serious	serious[1]	none	14	15	-	MD 7.9 lower (24.65	⊕OOO	CRITICAL

	trials	serious[2]	inconsistency	indirectness						lower to 8.85 higher)	VERY LOW	
Tinnitus severity (Tinnitus Magnitude Rating, 0-100 numeric rating scale) (post-treatment) (follow-up 2 weeks; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	18	17	-	MD 9.38 lower (22.89 lower to 4.13 higher)	⊕OOO VERY LOW	CRITICAL
Patient-reported subjective worsening of tinnitus (post-treatment) (follow-up 2 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[1]	none	4/18 (22.2%)	5/19 (26.3%)	RR 0.84 (0.27 to 2.66)	42 fewer per 1000 (from 192 fewer to 437 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias. Note: Difference in baseline outcome data – tinnitus severity (THI) - mean (SD): rTMS group 33.78 (22.15), sham group 39.30 (22.55); Tinnitus severity (Tinnitus Magnitude Rating) - mean (SD): rTMS group 51.11 (21.04), sham group 59.38 (17.5)

Table 19: Clinical evidence profile: Right dorsolateral prefrontal cortex (DLPFC) tDCS versus sham tDCS control for tinnitus

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Right dorsolateral prefrontal cortex (DLPFC) tDCS**	**Sham tDCS**	**Relative (95% CI)**	**Absolute**		
Tinnitus severity (Tinnitus Handicap Inventory) (post-treatment) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	21	21	-	MD 3.1 lower (13.52 lower to 7.32 higher)	⊕⊕⊕O MODERATE	CRITICAL
Tinnitus severity (Tinnitus Handicap Inventory) (3 month follow-up) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	21	21	-	MD 5.4 lower (18.05 lower to 7.25 higher)	⊕⊕⊕O MODERATE	CRITICAL

Tinnitus severity (Subjective Tinnitus Severity Scale) (post-treatment) (range of scores: 0-16; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	21	21	-	MD 0.5 lower (1.94 lower to 0.94 higher)	⊕⊕⊕O MODERATE	CRITICAL
Tinnitus severity (Subjective Tinnitus Severity Scale) (3 month follow-up) (range of scores: 0-16; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	21	21	-	MD 0.3 lower (1.87 lower to 1.27 higher)	⊕⊕⊕O MODERATE	CRITICAL
Tinnitus severity (tinnitus intensity on VAS) (post-treatment) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	21	21	-	MD 14.7 higher (-0.12 to 29.52 higher)	⊕⊕⊕O MODERATE	CRITICAL
Tinnitus severity (tinnitus intensity on VAS) (3 month follow-up) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	21	21	-	MD 0.8 higher (12.18 lower to 13.78 higher)	⊕⊕OO LOW	CRITICAL
Tinnitus severity (Clinical Global Impression Scale) (post-treatment) (range of scores: 0-7; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	21	21	-	MD 0 higher (0.34 lower to 0.34 higher)	⊕⊕⊕O MODERATE	CRITICAL
Tinnitus severity (Clinical Global Impression Scale) (3 month follow-up) (range of scores: 0-7; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	21	21	-	MD 0 higher (0.49 lower to 0.49 higher)	⊕⊕OO LOW	CRITICAL
Tinnitus distress (VAS) (post-treatment) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	21	21	-	MD 11 higher (3.6 lower to 25.6 higher)	⊕⊕⊕O MODERATE	CRITICAL
Tinnitus distress (VAS) (3 month follow-up) (range of scores: 0-100; Better indicated by lower values)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	21	21	-	MD 4.8 lower (18.91 lower to 9.31 higher)	⊕⊕⊕O MODERATE	CRITICAL
Tinnitus annoyance (numeric rating scale) (post-treatment) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	6	7	-	MD 16.1 higher (24.13 lower to 56.33 higher)	⊕OOO VERY LOW	CRITICAL
Tinnitus loudness (numeric rating scale 0-100) (post-treatment) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	6	7	-	MD 16.01 higher (13.94 lower to 45.96 higher)	⊕⊕OO LOW	CRITICAL
Anxiety and depression (Hospital Anxiety and Depression Scale) (1 month follow-up) (range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	21	21	-	MD 2.9 lower (7.2 lower to 1.4 higher)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 20: Clinical evidence profile: Left temporal area (LTA) tDCS versus sham tDCS for tinnitus

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Left temporal area (LTA) tDCS**	**Sham tDCS**	**Relative (95% CI)**	**Absolute**		
Tinnitus severity (Tinnitus Handicap Inventory) (post-treatment) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10	10	-	MD 4.5 higher (18.77 lower to 27.77 higher)	⊕OOO VERY LOW	CRITICAL
Tinnitus severity (Tinnitus Handicap Inventory) (2 weeks follow-up) (range of scores: 0-100; Better indicated by lower values)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10	10	-	MD 2.4 higher (21.55 lower to 26.35 higher)	⊕OOO VERY LOW	CRITICAL
Tinnitus distress (post-treatment) (range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10	10	-	MD 0.5 higher (1.26 lower to 2.26 higher)	⊕OOO VERY LOW	CRITICAL
Tinnitus distress (2 week follow-up) (range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10	10	-	MD 0.8 higher (1.22 lower to 2.82 higher)	⊕OOO VERY LOW	CRITICAL
Tinnitus loudness (post-treatment) (range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10	10	-	MD 0.2 lower (2.22 lower to 1.82 higher)	⊕OOO VERY LOW	IMPORTANT
Tinnitus loudness (2 weeks follow-up) (range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10	10	-	MD 0.3 higher (2.03 lower to 2.63 higher)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 21: Clinical evidence profile: VNS versus sham VNS for tinnitus

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Vagal Nerve Stimulation (VNS)**	**Sham VNS**	**Relative (95% CI)**	**Absolute**		
Tinnitus severity (Tinnitus Handicap Inventory) (post-treatment) (range of scores: 0-100; Better indicated by lower values)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	16	14	-	MD 10.4 lower (32.26 lower to 11.46 higher)	⊕⊕⊕O MODERATE	CRITICAL
Tinnitus severity (Tinnitus Handicap Questionnaire) (post-treatment) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	16	14	-	MD 5 higher (4.66 lower to 14.66 higher)	⊕⊕⊕O MODERATE	CRITICAL
Tinnitus severity (Tinnitus Functional Index) (post-treatment) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	16	14	-	MD 5.47 higher (3.87 lower to 14.81 higher)	⊕⊕⊕O MODERATE	CRITICAL
Tinnitus loudness (post-treatment) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	16	14	-	MD 1.81 higher (13.22 lower to 16.84 higher)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

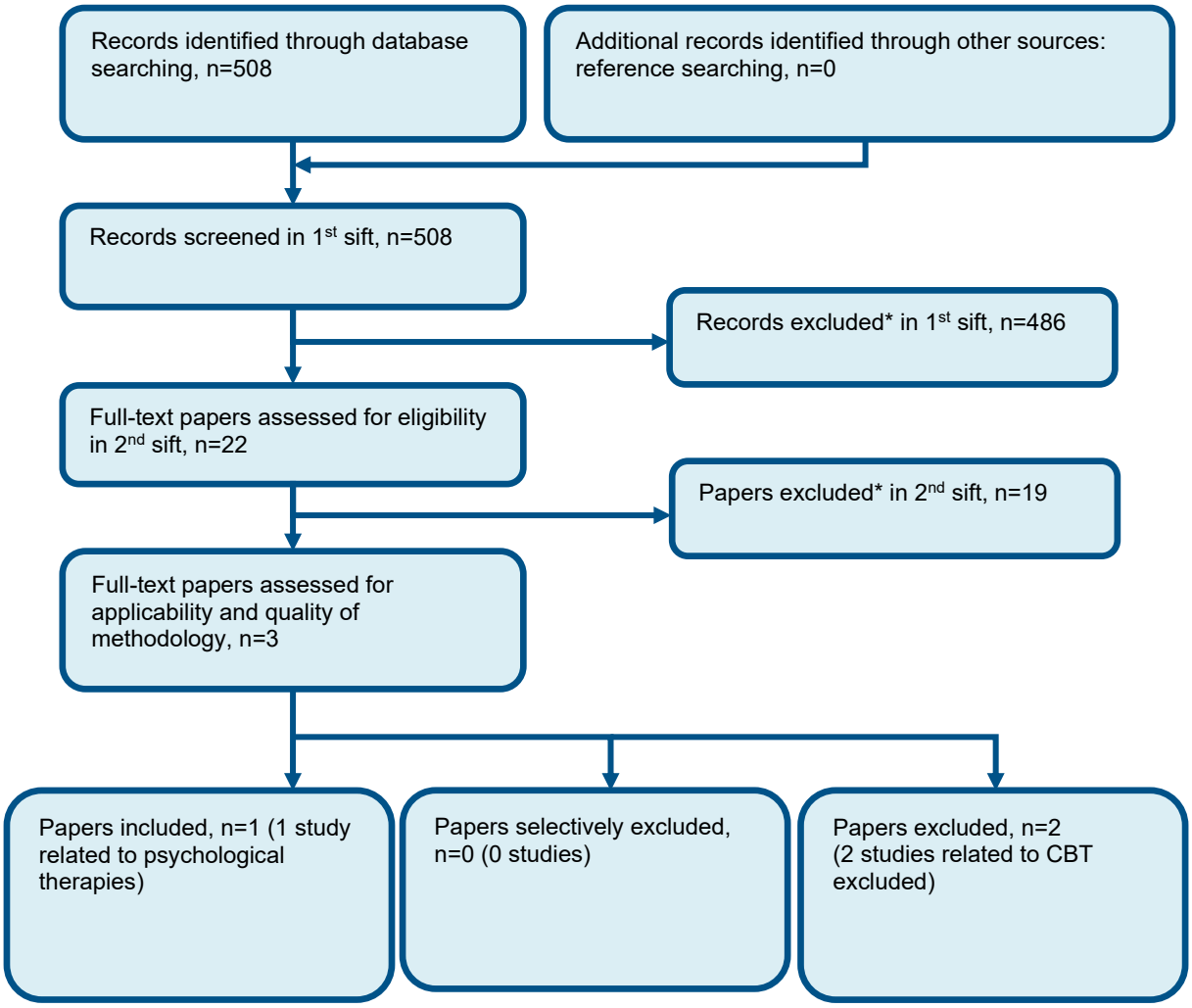
Table 22: Clinical evidence profile: Acoustic CR versus sham acoustic CR for tinnitus

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Acoustic CR neuromodulation**	**Sham acoustic CR**	**Relative (95% CI)**	**Absolute**		
Tinnitus severity (Tinnitus Questionnaire) (post-treatment) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	serious[3]	no serious inconsistency	serious[1]	very serious[2]	none	58	5	-	MD 2.37 lower (9.17 lower to 4.43 higher)	⊕OOO VERY LOW	CRITICAL
Tinnitus severity (Tinnitus Questionnaire) (4 week follow-up) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	serious[3]	no serious inconsistency	serious[1]	very serious[2]	none	58	5	-	MD 2.58 lower (12.34 lower to 7.18 higher)	⊕OOO VERY LOW	CRITICAL

Tinnitus annoyance (post-treatment) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	serious[3]	no serious inconsistency	serious[1]	serious[2]	none	58	5	-	MD 13.21 lower (28.75 lower to 2.33 higher)	⊕OOO VERY LOW	CRITICAL
Tinnitus annoyance (4 week follow-up) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	serious[3]	no serious inconsistency	serious[1]	very serious[2]	none	58	5	-	MD 12.61 lower (42.62 lower to 17.4 higher)	⊕OOO VERY LOW	CRITICAL
Tinnitus loudness (post-treatment) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	serious[3]	no serious inconsistency	serious[1]	very serious[2]	none	58	5	-	MD 3.01 lower (20.41 lower to 14.39 higher)	⊕OOO VERY LOW	IMPORTANT
Tinnitus loudness (4 week follow-up) (range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	serious[3]	no serious inconsistency	serious[1]	very serious[2]	none	58	5	-	MD 10.19 lower (36.13 lower to 15.75 higher)	⊕OOO VERY LOW	IMPORTANT

[1] The majority of the evidence is pooled from one study in which four different treatment types/protocols (featuring different frequencies of intervention and different intervention lengths) were used
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias. Note: Significant outcome differences at baseline, Tinnitus Questionnaire score 0-100 (mean): Acoustic CR group 42.25, sham group 29.2; Significant outcome differences at baseline, tinnitus annoyance score 0-100 (mean): Acoustic CR group 63.9, sham group 38.0; Significant outcome differences at baseline, tinnitus loudness score 0-100 (mean): Acoustic CR group 65.35, sham group 43.0

Appendix G: Health economic evidence selection



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H: Excluded studies

H.1 Excluded clinical studies

Table 23: Studies excluded from the clinical review

Study	Exclusion reason
Abtahi 2018[1]	Inappropriate comparison (do not describe what the control is)
Cavalcanti 2015[4]	No extractable outcome data. Letter to editor
D'arcy 2017[6]	Incorrect study design: protocol
Dobie 1986[7]	No extractable outcome data
Engelhardt 2014[8]	Inappropriate comparison (no control).
Forogh 2014[12]	Inappropriate comparison (no control, compares two rTMS protocols)
Garin 2011[13]	No extractable outcome data
Haller 2017[15]	No extractable outcome data
Henin 2016[16]	Incorrect interventions (compares compensatory auditory stimulation versus tDCS, or combined versus sham). No relevant outcomes
Hyvarinen 2016[17]	Incorrect study design (non-randomised study)
Kapkin 2008[18]	No relevant extractable outcome data
Khedr 2008[20]	Results not extractable
Khedr 2010[19]	Inappropriate comparison (compares two forms of rTMS)
Kim 2014[21]	Inappropriate comparison (compares two forms of rTMS)
Kim 2014[22]	Inappropriate comparison (compares two forms of rTMS)
Kreuzer 2015[23]	Inappropriate comparison (compares two forms of rTMS)
Lee 2014[26]	Incorrect interventions (TENS, not in protocol)
Li 2015[28]	Incorrect study design: study protocol
Li 2019[27]	Incorrect interventions (TENS, not in protocol)
Mei 2014[30]	Incorrect interventions. Electrical stimulation + acupuncture
Meng 2011[31]	Cochrane review, not all papers includable
Mennemeier 2011[32]	No relevant extractable outcome data
Mielczarek 2014[33]	Incorrect interventions (hydrotransmissive electrical stimulation). No relevant extractable outcome data
Piccirillo 2011[36]	No relevant extractable outcome data
Rashidi 2018[37]	Study protocol
Roland 1993[39]	Results not extractable
Roland 2016[38]	No relevant extractable outcome data
Rossi 2007[40]	Incorrect study design: crossover study
Sahlsten 2019[41]	Inappropriate comparison (compared two forms of rTMS). Incorrect interventions
Shekhawat 2014[43]	Data not extractable
Smith 2007[45]	Incorrect study design: crossover study
Stein 2016[46]	Incorrect interventions (tailor-made notched music training)
Teismann 2014[48]	Incorrect interventions. Combination intervention (tailor-made notched music training plus tDCS)
Theodoroff 2017[49]	No relevant extractable outcome data
To 2017[50]	Data not extractable

Study	Exclusion reason
Vanneste 2013[52]	No relevant extractable outcome data
Wang 2018[53]	Systematic review
Wegger 2017[54]	Systematic review
Wobrock 2006[55]	Not in English
Wurzer 2018[56]	Inappropriate comparison (no control). Incorrect interventions (hearing threshold adapted coordinated reset)
Yadollahpour 2017[57]	No extractable outcome data

H.2 Excluded health economic studies

None.

Appendix I: Research recommendations

I.1 Neuromodulation

Research question: What is the clinical, cost effectiveness and safety of neuromodulation interventions for treating tinnitus in adults?

Why this is important:

Neuromodulation therapies aim to reduce tinnitus perception by normalising pathological synchronous neural activity using electrical, acoustic and/or magnetic energy. They offer a set of interventions for the management of tinnitus and are currently not offered on the NHS. The limited evidence base and lack of research into long-term effects prevent a meaningful recommendation from being made. Further studies are therefore required to establish the clinical- and cost-effectiveness of neuromodulation interventions for tinnitus.

Criteria for selecting high-priority research recommendations:

PICO question	Population: Adults with tinnitus Intervention(s): • Acoustic coordinated reset (CR) neuromodulation • Electrical stimulation with sound therapy • Repetitive transcranial magnetic stimulation (rTMS) • Transcranial direct current stimulation (tDCS) • Transcranial alternating current stimulation (tACS) • Vagal nerve stimulation (VNS) • Transcutaneous vagal nerve stimulation (tVNS) Comparison: Sham intervention Outcome(s): A focus should be on outcomes at long-term follow-up (e.g. minimum of 1 year) Health related QoL: (critical) • QoL (EQ-5D) Impact of tinnitus, measured using validated questionnaires: (critical) • Tinnitus Distress • Tinnitus Annoyance Adverse events (critical) • Safety • Tolerability/adherence/drop-outs/attrition • Side effects (e.g. worsening of tinnitus) Tinnitus percept, measured using validated questionnaires: • Tinnitus Loudness (important) Other co-occurring complaints, measured using validated questionnaires

	(important) • Depression • Anxiety • Anxiety and depression • Sleep
Importance to patients or the population	A successful new intervention in this area could offer a method to improve quality of life and reduce tinnitus distress. Some people with tinnitus may prefer these tools to others interventions in current practice (e.g. CBT). There is also the potential of cost and time saving to the NHS if a device was efficacious and offered at an acceptable cost per QALY level.
Relevance to NICE guidance	This is an emerging area of potential treatment and management of tinnitus with growing interest from the clinical, research and patient populations. There is potential to prove or disprove a range of treatments and create the foundation for strong NICE recommendations in the future.
Relevance to the NHS	This is a heterogeneous group of treatments, none of which are currently offered for tinnitus on the NHS. Some of these treatments have the potential to be offered as highly cost-effective treatments for the management of tinnitus if demonstrated as clinically effective.
National priorities	N/A
Current evidence base	The current evidence base is very poor. Sixteen studies were found to meet the criteria for inclusion in the review and of these the majority of evidence was judged low or very low quality and were heterogeneous. Considering the volume of research conducted in this area it is disappointing that the committee felt it was unable to make a practice recommendation on any of the interventions. There is an urgent need for high quality randomised controlled trials.
Equality	N/A
Study design	Randomised blinded control trials (with sham intervention). Short (up to one month), medium (up to 6 months) and longer term outcomes (more than 1 year), particularly related to side-effects, should be investigated following the intervention.
Feasibility	The committee believes it is possible to carry out this research in a realistic timescale and at an acceptable cost, if done well. The only ethical question raised is of long-term safety.
Other comments	There is currently limited evidence for the long-term safety of neuromodulation interventions for the treatment of tinnitus. This should be addressed in future research, with a focus on long-term safety and side effect outcomes. This research recommendation is restricted to adults suffering with tinnitus; further evidence of safety is required in order to recommend future studies in children and young people with tinnitus.
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.