| Table E2. Medical interventions and outcomes (n=11) | | | | | | | |
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| **Author**  **Year**  **Setting** | **Population Description** | **Intervention** | | **Outcome Measures** | | **Results** | |
| Anders,73  2010  Czech Republic | Baseline sample: Total n = 52;  Interven n = 26; Cntrl n = 26  Setting: Outpatient Otorhinolaryngology clinic  Mean age (SD):  Interven: 48.1y (14.86);  Cntrl: 50.1y (13.97)  Gender: 69% male  Presumed etiology of tinnitus: Idiopathic  Duration of tinnitus: > 6 months  Severity of tinnitus: Uni- or bilateral tinnitus according to KD-10, no response to >3 months of pharmacological treatment  Number of dropouts: 10  Reasons for dropouts: Treatment n = 4; worsening of tinnitus (2); adverse events(2)  Cntrl n = 6; lack of efficacy (3); adverse events (2); unknown (1)  Audiological factors: Included age-adjusted normal sensorineural hearing. Excluded profound hearing loss or Meniere’s disease  Comorbidities: NR | | Repetitive Transcranial Magnetic Stimulation (rTMS)  Patients were treated with either real or sham low frequency rTMS over a period of 2 weeks. Blinding design applied.  Comparator: Placebo  Duration of treatment: 2 weeks  Number of follow ups: 4  Duration of study: 6 months | | TS-QOL  (THI\*, TQ-mod, VAS) | | The ability to reduce the symptoms of the tinnitus appeared in both randomized groups immediately after the 1 Hz rTMS and sham stimulation phase. There was a significant reduction in both groups of the tinnitus total score on the Tinnitus Handicap Inventory (THI) (real rTMS p=0.00t; sham rTMS p=0.049).  Reduction of symptoms as evaluated using the TQ was significant compared to baseline in the real rTMS group at week 2, 6 and 14 (p=0.003; p=0.024; p=0.022).  Real 1 Hz rTMS treatment was capable of significantly reducing the total baseline score of basic scales that measure tinnitus severity. Important for patients with long-term symptoms resistant to pharmacological treatment.  Adverse Events: unacceptable pain in stimulation area, headache, lack of efficacy and subjective worsening of tinnitus | |

| **Table E2. Medical Interventions and outcomes (n=11) (continued)** | | | | |
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| **Author**  **Year**  **Setting** | **Population Description** | **Intervention** | **Outcome Measures** | **Results** |
| Chung,79  2012  China | Baseline sample: Total n = 22  Intervention n = 12  Cntrl n = 10  Setting: University medical Hospital  Total Mean age:  52.96 (range 20-76 yrs)  Gender:  Int 91.6% male Cntrl 90.0% male  Presumed etiology of tinnitus:  Duration of tinnitus: :  Int range 0.5 to 20 years  Cntrl: 2 to 10 years  Severity of tinnitus: Mean score on TQ and THI  Number of dropouts: 0  Reasons for dropouts: NA  Audiological factors: Most subjects had unilateral problems  Comorbidities: Excluded subjects with known history of metal implants, head injury, stroke, epilepsy | Intervention: rTMS coil was placed over the auditory cortex with the intensity setting at 80% of the resting motor threshold. 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.  Comparator: Sham rTMS  Duration of treatment: Once daily for 10 consecutive days  Number of followups: 1 week and 1 month post treatment.  Duration of study: NR | TS-QOL  (THI\*, TQ)  Loudness (VAS) | 9/12 patients (75%) in the active-stimulation group reported tinnitus suppression following treatment with rTMS.  TQ global scores averaged 8.58 points lower 1 week after treatment, a significant decrease compared to the sham-stimulation group  (p <0.01).  THI scores were, on average, 8.33 points lower after treatment, which were also significantly lower than those of patients in the sham-stimulation group (p <0.01).  Tinnitus loudness also decreased significantly after delivering rTMS. (p<0.05)  Adverse Events: No patients experienced sustained side effects after the rTMS treatment. |
| Cuda,80  2008  Italy | Baseline sample: Total n = 46  Interven n = 26; Cntrl n = 20  Setting: University Otolaryngolgy clinic  Mean age (SD): 56.4y (13.6)  Int: 50.3y (9.8); Cntrl: 64.4y (14.1)  Gender: 58.7 % male  Presumed etiology of tinnitus: non-intermittent subjective tinnitus  Duration of tinnitus: mean 6.4 years (8.8)  Severity of tinnitus: ‘disturbing’ > 3 months  Number of dropouts: None  Reasons for dropouts: NA  Audiological factors: 60.9% had no clinically significant hearing impairment  Comorbidities: NR | Low Level Laser Stimulation + combined counseling protocol (LLS+). Emission power was 5mW, and the wavelength was 650nm. Patients trained to use the device for 20 minutes per day, each day for 3 months.  Comparator: combined counseling protocol with sham LLS (LLS-)  Combined Counseling consisted of a combination of hypnotic techniques with relations techniques based on respiration, proprioception and insight  Duration of treatment: 3m  Number of followups: 10  Duration of study: NR | TS-QOL  (THI) | Approximately 61% of irradiated patients had tinnitus severity decreased by one class, in comparison to 35% of the placebo group.  This study confirmed a significant difference in the benefit of treatment between the LLS+ and LLS- groups.  Adverse events: NR |
| Ghossaini,85  2004  United States | Baseline sample Total n = 29  Interven n = 15; Cntrl n =14  Setting: NR  Age: Range 23 to 83 y  Gender: NR  Etiology of tinnitus: cause/origin of tinnitus in the study sample varied  Duration of tinnitus: 7 months to 60 y  Severity of tinnitus: Chronic >6 months  Number of dropouts: 2  Reasons for dropouts: Failure to return for post-treatment testing (not included in analysis)  Comorbidities: NR | High-Frequency Pulsed Electromagnetic Energy (Diapulse)  Patients received 30-minute treatments with the Diapulse device (model D103) 3 times per week for 1 month.  Comparator: placebo (deactivated machine)  Duration of treatment: 1 month  Number of follow-ups: NA  Duration of study: NR | TS-QOL  (THI\*, TMR) | There was no significant change in the pre-treatment and post-treatment audiometric thresholds in either group.  There were no significant differences between the pretreatment and post-treatment THI scores or the tinnitus rating scores in either subject group  Adverse Events: tingling (Treatment) and worsening of tinnitus (5 Control; 4 Treatment) |
| Langguth,94  2008  Germany | Baseline sample: Total n = 32  Interven n = 16; Cntrl n = 16  Setting: Dept. of Psychiatry  Mean age (SD): 51.5y (11.6)  Int: 52.6y (12.6); Cntrl: 50.3y (10.8)  Gender: 71.8% male  Int: 81.3% male; Cntrl: 62.5% male  Presumed etiology of tinnitus: NR  Duration of tinnitus:  Int: 10.9y (10.1); Cntrl: 11.7y (10.9)  Severity of tinnitus: ‘disturbing’ tinnitus  Number of dropouts: None  Reasons for dropouts: NA  Audiological factors: normal middle-ear status  Comorbidities: all had tried several standard treatment modalities | To investigate whether priming stimulation enhances the efficacy of low-frequency rTMS. Medtronic  Interven: Priming protocol (960 stimuli; 6 Hz + 1040 stimuli; 1 Hz)  Comparator: standard protocol (2000 stimuli; 1 Hz)  Duration of treatment: 10 working days  Number of followups: 4 over 13 weeks  Duration of study: NR | TS-QOL  (TQ) | There was no significant difference between the standard protocol and the protocol involving priming stimulation.  Data does not support an enhancing effect of higher frequency priming on low-frequency rTMS in the treatment of tinnitus.  Adverse Events: No serious adverse or side effects were observed |
| Marcondes,96  2010  Spain | Baseline sample: Total n=19  Interven=10  Cntrl=9  Setting: Otohinolaryngology clinic  Mean Age: NR  Gender: NR  Presumed etiology of tinnitus: Idiopathic  Duration of tinnitus: > 3 months  Severity of tinnitus: NR  Number of dropouts: 1  Reasons for dropouts: 1 participant withdrew consent before treatment began Audiological factors: Hearing lever in tinnitus ears – data presented by ear  Comorbidities: NR | Repetitive Transcranial Magnetic Stimulation: 5 sessions of rTMS performed on 5 consecutive days  Comparator: Placebo  Duration of treatment: 5 days  Number of follow ups: 10  Duration of study: 6 months | TS-QOL  (THI) | Significant improvement of the tinnitus score in the active rTMS group as compared to sham rTMS for up to 6 months after stimulation. SPECT measurements demonstrated a reduction of metabolic activity in the inferior left temporal lobe after active rTMS.  Results demonstrate a significant reduction of tinnitus complaints over a period of at least 6 months and significant reduction of neural activity in the inferior temporal cortex.  Adverse Events: no relevant side effects |
| Mirz,99  1999  Denmark | Baseline sample: Total n = 50  Interven n = 25; Cntrl n = 25  Setting: otorhinolaryngology clinic  Mean age (SD):  Interven n = 48.6 y; Cntrl n = 48.7 y  Gender: Total: 75.5% male  Interven: 64.0% male; Cntrl: 87.5% male  Presumed etiology of tinnitus: Idiopathic Duration of tinnitus: Mean 5.5y  Severity of tinnitus: Disabling, chronic  Number of dropouts: 1  Reasons for dropouts: Unrelated illness  Audiological factors: sensorineural hearing loss  Comorbidities: NR | Laser Therapy vs Placebo  The active laser applied 50mW (cw, 830 nm) over a period of 10 min per session. The laser treatment consisted of three periods of five consecutive days separated by weekends, totaling 15 treatment sessions.  Comparator: Placebo – an identical looking laser probe was inactivated by the producer  Duration of treatment: 5 week days  Number of follow ups: 4  Duration of study: | Anxiety (STAI)  Depression (BDI)  Loudness (VAS)  TS-QOL  (THI\*, VAS-Ann, VAS-Att) | The results showed only moderate (18%) subjective improvement with no statistically significant differences between the effects of the active laser and placebo treatment.  There were no statistically significant differences in pre-post measurements of tinnitus loudness, VAS scores, THI scores, or TCSQ scores for patients treated with active laser compared with those treated with placebo.  Adverse Events: No serious untoward adverse or side effects were noticed |
| Plewnia,102  2012  Germany | Baseline sample: Total n = 48  Interven1 (SAC) n = 16  Interven2 (TAC) n = 16  Cntrl (PLC) n = 16  Setting: University Psychiatry and outpatient clinic Department of Otorhinolaryngology  Mean age (SD):  SAC: 46.4y (13.0); TAC: 55.8y (9.7);  PLC: 45.6y (10.3)  Gender:  SAC 10.5%male; TAC 43.8%male;  PLC 50%male  Presumed etiology of tinnitus: NR  Duration of tinnitus: < 5y chronic tinnitus  Severity of tinnitus: NR  Number of dropouts: total n = 8;  SAC n = 4; TAC n = 2; PLC n= 2  Reasons for dropouts: Tinnitus worsening (4); Patient decision (3); sudden hearing loss (1)  Audiological factors:  Comorbidities: | 4 weeks of bilateral cTBS to the secondary auditory cortex (SAC) and temporoparietal cortex (TAC)  Stimulation (cTBS) intensity was standardized at 80% AMT  Each stimulation train (40 s) consisted of 600 stimuli applied in bursts of 3 pulses at 50 Hz given every 200 msec (i.e., at 5 Hz). Fifteen minutes after the first 2 trains, a second pair of cTBS trains was given (a total of 2,400 stimuli/day). Patients received cTBS treatment each working day for 4 weeks (20 sessions) the 10–20 EEG electrode placement system was used to localize Brodmann area 39 (TAC: halfway between T5/P3 and T6/P4) and Brodmann area 42/22 (SAC: halfway between T3/C3 and T4/C4).  For adequate masking of the patients, sham stimulation (PLC) was performed behind the mastoid.  Comparator: sham stimulation (PLC)  Duration of treatment: 4 weeks  Number of followups: 1 (12 weeks)  Duration of study: Feb 2008 to May 2010 | TS-QOL (TQ) | Tinnitus severity was slightly reduced from baseline by a mean (SD) 2.6 (8.2) after sham, 2.4 (8.0) after temporoparietal, 2.2 (8.3) after temporal treatment of 16 patients each, but there was no significant difference between sham treatments and temporal (confidence interval [CI] -5.4 to +6.7) or temporoparietal cTBS (CI -5.9 to +6.3) or real cTBS (CI -7 to +5.1).  Patients’ global evaluation of tinnitus change after treatment did not indicate any effects.  Adverse events:  Patients reported the following side effects: headache (SAC: 2, TAC: 2, PLC: 3), worsening of tinnitus (SAC: 1, TAC: 2, PLC: 3), increased sensitivity to noise (TAC: 1, PLC: 1), painful local sensation (SAC: 1), and sleep disturbance (SAC: 1). An acute hearing loss associated with increased tinnitus loudness was observed in 1 patient after session 17 (SAC). In this patient, hearing thresholds and tinnitus returned to baseline after 3 weeks. |
| Tass,108  2012  Germany | Baseline sample: Total n=63  Interven (4 groups) G1 n = 22; G2 n = 12; G3 n = 12; G4 n = 12  Cntrl (G5) n = 5  Setting: 2 treatment centers in Germany  Mean age (SD): >18  G1: 45.7 (10.8); G2 47.7 (5.6); G3 50.0 (14.7); G4 50.3 (11.8); G5 57.6 (6.3)  Gender:  G1: 72.7% male; G2: 83.3% male; G3: 50.0% male; G4: 75.0% male; G5: 60.0% male  Presumed etiology of tinnitus: chronic tonal tinnitus  Duration of tinnitus [years – Mean (SD)]: all >6 months  G1: 5.7 (5.1); G2: 6.6 (6.0); G3: 5.4 (3.5);  G4: 7.9 (9.8); G5: 11.3 (5.6)  Severity of tinnitus: chronic  Number of dropouts: 0  Reasons for dropouts: N/A  Audiological factors: Morbus Meniere, TMJ, psychiatric disorders and objective tinnitus excluded  Comorbidities: NR | Acoustic Coordinated Reset (CR) neuromodulation: 4 stimulation groups. For G1, G3 and G4 four tones (top, f1 to f4) are grouped around the tinnitus frequency (ft). G3 differs only in repetition rate F being adapted to the individual EEG § -band peak.  For G2 each CR cycle is formed by a varying composition of four tones (dark green: active) chosen out of twelve tones (middle, f1 to f12) surrounding ft.  Comparator: Placebo stimulation (G5) is formed similar to G1 using a down-shifted stimulation-frequency fp (fp = 0.7071·ft/ (2n), fp within [300 Hz, 600 Hz]) outside the synchronized tinnitus focus.  Duration of treatment: G1 to G3 received stimulation for 4 to 6 hours every day for 12 weeks applied either continuously or split into several sessions not shorter than 1 hour  G4 and G5 all received stimulation for 1 hour max. every day  Number of followups: 1,4,8, 12 and 16 weeks after beginning of treatment and every 4 weeks during optional 24 week LTE  Duration of study: NR | TS-QOL  (TQ\*, VAS)  Loudness (VAS) | Strong and significant reduction of VAS loudness in G1 and G3 in the on-stimulation condition (p≤0.01)  G1 also significant compared to placebo (G5) (p<0.05)  A reduction of at least 6 TQ points was obtained in 75% of patients with a mean TQ reduction of 50% among responders.  Adverse events – 15 AEs: 13 AEs during blinded phase, 2 AEs in LTE.  2 SAEs not associated with treatment were reported; All other AEs were of mild to moderate intensity and none was permanent.  8 AEs were judged to be treatment related of which 3 AEs were associated with a transient increase of tinnitus loudness |
| Teggi,31  2009  Italy | Baseline sample Total n = 60  Interven: n = 30; Cntrl n = 30  Setting: ENT department  Mean age (SD):  Interven: 51.6y (11.3);  Cntrl: 53.1y (12.9)  Gender:  Interven: 59.2% male;  Cntrl: 51.2% male  Presumed etiology of tinnitus: NR  Duration of Tinnitus: NR  Severity of tinnitus: NR  Number of dropouts: Interven n = 3; Cntrl n = 3  Reasons for dropouts: familial reasons (4), increase in tinnitus loudness (2)  Audiological factors: NR  Comorbidities: NR | Laser Therapy  All patients instructed to perform laser therapy with the TinniTool soft laser at home for 20 min a day for a period of 3 months; patients in the first group (group L) received an active laser  Comparator: Placebo - a dummy laser (group C).  Duration of treatment: 3 months  Number of follow ups: 1  Duration of study: NR | TS-QOL  (THI)  Loudness (VAS) | No statistical difference was detected between the 2 groups in the THI total score (p = 0.97), and the functional (p = 0.89), emotional (p = 0.89) and catastrophic (p = 0.89) subscales. VAS for self-perceived loudness of the tinnitus showed no difference between the groups (p = 0.69).  Soft laser therapy demonstrated no efficacy as a therapeutic measure for tinnitus in this report.  Adverse Events: subjects with migraine presenting hyperacusis (Treatment = 4; Control = 2).  Increase in loudness (Treatment = 1; Control = 1) |
| Vilholm,110  1998  Denmark | Baseline sample Total n = 54  Interven n = 29; Cntrl n = 25  Setting: Department of Audiology  Mean Age (SD): 53.1 y  Gender:  Int: 68.9% male; Cntrl: 60.0% male  Presumed etiology of tinnitus: Idiopathic Duration of tinnitus: ≥ 1 yr Severity of tinnitus: Severe treatment-resistant tinnitus  Number of dropouts: 0  Reasons for dropouts: N/A Audiological factors: NR Comorbidities: NR | Acupuncture vs Placebo  Acupuncture group treated with traditional Chinese acupuncture of 25 treatment sessions over 2 months. Sessions distributed over 3 treatment periods of 10, 5 and 10 treatments separated first by a pause of one week, and then by a pause of two weeks. Treatment given each day for 30 minutes.  Comparator: Placebo group treated with placebo acupuncture.  Duration of treatment: 4 months  Number of follow ups: 2  Duration of study: NR | TS-QOL  (VAS-Ann\*, VAS-Awr)  Loudness (VAS) | No statistically significant differences were found between the acupuncture group and the placebo group.    Adverse Events: NR |

\*Indicates the test used to measure outcomes which were selected to represent the domain in the forest plots (and subsequent SOE decisions)  
**Abbreviations:** A/E = Adverse events; AMT = active motor threshold; CBT = cognitive behavioral treatment; ENT = ear, nose and throat; G1 to G5 = group; G-QOL = global quality of life; HADS = Hospital Anxiety and Depression Scale; interven = Intervention; month = month; N/A = not applicable; NR = not reported; QOL = quality of life; RCT = randomized Controlled trial; SD = standard deviation; TCT = Tinnitus Coping Therapy; THI = Tinnitus Handicap Inventory; TMJ = temporal mandibular joint; TS = tinnitus specific; TSQ = Tinnitus Severity Questionnaire; VAS = visual analog scale; week = week; WLC = wait list Cntrl; yr = year