National Institute for Health and Care Excellence

Draft

Chronic pain: assessment and management

[H] Evidence review for electrical physical modalities

NICE guideline

Intervention evidence review underpinning recommendation 1.3.6 and the research recommendation in the NICE guideline

August 2020

Draft for Consultation

This evidence review was developed by the National Guideline Centre

Disclaimer

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1 Electrical physical modalities for chronic primary pain

1.1 Review question: What is the clinical and cost effectiveness of electrical physical modalities for the management of chronic primary pain?

1.2 Introduction

Electrical physical modalities of treatment have been used therapeutically for many centuries. Reports of their use have been found in ancient writings, and include techniques still in use today, such as use of heat, cold and electricity.

Contemporary electrical physical modalities are diverse and include treatments regularly used for pain management and self-management. The list below is not exhaustive:

- Thermal modalities, often in the form of reusable hot or cold packs applied to the skin.
- Therapeutic ultrasound, using a probe that generates ultrasonic waves from electricity and delivers them into the tissues.
- Interferential therapy, using medium frequency electrical currents delivered with multiple electrodes over the affected areas.
- Pulsed Shortwave Diathermy, using high frequency electromagnetic energy delivered using electrical coils, to heat the tissues.
- Low level laser therapy (LLLT), involving the non-invasive application of a single wavelength of light to the skin over the injured area using a probe.
- Neuromuscular Electrical Stimulation (NMES), using superficial electrodes to target motor fibres.

For many of these techniques, a mechanism of action is currently unclear. Mechanisms may include activation of pain gate mechanisms, stimulation of cellular activity related to healing and repair, delivery of mechanical forces to alter the physical properties of tissues, alteration of blood flow and reduction of inflammation.

While many of these interventions are popular choices for the self-management of painful conditions, their role in clinical practice is much less clear. This evidence review therefore intends to explore the effectiveness of these interventions for chronic primary pain.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	People, aged 16 years and over, with chronic primary pain (whose pain management is not addressed by existing NICE guidance) (chronic widespread pain, complex regional pain syndrome, chronic visceral pain, chronic orofacial pain, chronic primary musculoskeletal pain other than orofacial) Chronic pain in one or more anatomical regions that is characterized by significant emotional distress (anxiety, anger/frustration or depressed mood) and functional disability (interference in daily life activities and reduced participation in social roles). The diagnosis is appropriate independently of identified biological or psychological contributors unless another diagnosis would better account for the presenting symptoms.

Interventions	Interventions: • Transcutaneous electrical nerve stimulation (TENS) • Percutaneous electrical nerve stimulation (PENS) • Interferential therapy • Laser therapy • Therapeutic ultrasound • Transcranial magnetic stimulation (TMS) • Transcranial direct current stimulation (TDCS).
Comparisons	Comparators: • Each other • Placebo/sham • Usual care • Physical therapies in this guideline.
Outcomes	Outcomes will be extracted at the longest time point up to 3 months and at the longest time point after 3 months. CRITICAL: • Pain reduction (any validated scale) • Health related quality of life (including meaningful activity) • Physical function (5 minute walk, sit to stand, Roland Morris Disability Questionnaire, Oswestry Disability Index, Canadian Occupational Performance Measure) • Psychological distress (depression/anxiety) (preferably Hospital Anxiety and Depression Scale) • Pain interference (brief pain inventory interference subscale) • Pain self-efficacy (pain self-efficacy questionnaire). IMPORTANT: • Use of healthcare services • Sleep • Discontinuation.
Study design	Randomised controlled trials (RCTs) and systematic reviews of RCTs. Cross-over RCTs will be considered if no non-cross-over RCT evidence is identified.

1.4 Clinical evidence

1.4.1 Included studies

34 studies were included in the review; [19, 28, 31, 37, 53, 61, 77, 78, 92, 94, 96, 101, 117, 120, 129, 137, 147, 167, 176, 185, 205, 241, 250, 274, 289, 314, 325, 329, 339, 345, 346, 354, 375] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary tables below (Table 3, Table 4, Table 5, Table 6, Table 7: Clinical evidence summary: TENS versus usual care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute Risk with Control
Quality of life at ≤3 months (SF36 physical component T scores, high is good outcome, change scores)	202 (1 study) 4 weeks	⨁⨁⨁⊖ MODERATE1 due to risk of bias		The mean change in quality of life score in control groups was 1.4

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute Risk with Control
Quality of life at ≤3 months (SF36 mental component T scores, high is good outcome, change scores)	202 (1 study) 4 weeks	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean change in quality of life score in control groups was 0.04
Pain reduction at ≤3 months (BPI intensity, 0-10, high is poor outcome, change scores)	242 (2 studies) 4-10 weeks	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean change in p score in the control groups was 0.15
Physical function at ≤3 months (6 minute walk test, feet walked, change scores)	202 (1 study) 4 weeks	⊕⊕⊕⊕ HIGH		The mean change physical function in th control groups was -42.1
Psychological distress at ≤3 months (PROMIS depression T scores, high is poor outcome, change scores)	202 (1 study) 4 weeks	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean change in psychological distress the control groups wa 0.4
Psychological distress at ≤3 months (PROMIS anxiety T scores, high is poor outcome, change scores)	202 (1 study) 4 weeks	⊕⊕⊕⊖ MODERATE1 due to risk of bias		The mean change in psychological distress the control groups wa -0.7
Pain interference at ≤3 months (BPI interference 0-10, high is poor outcome, change scores)	202 (1 study) 4 weeks	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean change in p interference in the co groups was -0.3
Pain self-efficacy at ≤3 months (PSEQ 0-60, high is good outcome, change scores)	202 (1 study) 4 weeks	⊕⊕⊕⊕ HIGH		The mean change in p self-efficacy in the co groups was 0.8

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

Table 8, Table 8, Table 10). 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 F.

1.4.2 Excluded studies

A Cochrane review of TENS for fibromyalgia was identified (Johnson 2017 [174]), and references were cross-checked with this review. However, the review was not included because it deviated from the protocol of this review as it included crossover studies and studies that compared to other interventions, for example pharmacological.

See the excluded studies list in appendix I.

1.4.8 Summary of clinical studies included in the evidence review

2 **Table 2: Summary of studies included in the evidence review**

Study	Intervention and comparison	Population	Outcomes	Comments
Altan 2005[19]	2 week interventions **Intervention 1: Laser therapy (n=26)** **Number of sessions**: 10 (over 2 weeks) **Duration of sessions**: Not reported (2mins per trigger point) **Delivered by**: Not reported **Details**: Laser applied over each trigger point for 2 minutes, frequency 1000Hz frequency, 904nm wavelength, maximum power 50W. Participants instructed to perform daily isometric exercises and stretching at home **Intervention 2: Sham laser therapy (n=27)** Details: identical treatment but laser not turned on.	Myofascial pain (n=53) Mean age: 43.4 (2.26) years Duration of pain: 4.56 (1.26) years	At 2 weeks post-intervention and 3 months (follow up, including 2-week intervention): • Pain reduction	Myofascial pain definition: localised pain and taut bands in the neck for a minimum of the previous 3 months, tenderness in the cervical trigger points.
Arbabi-Kalati 2015[28]	2 week interventions **Intervention 1: Laser therapy (n=10)** **Number of sessions**: 4 (over 2 weeks) **Duration**: Estimated 1.5 minutes (laser applied for 10s to 10 areas) **Delivered by:** Not reported **Details**: 630nm wavelength, 30mW power, low level laser therapy applied to oral mucosa. **Intervention 2: Sham laser therapy (n=10)** **Details**: Identical treatment but laser not turned on.	Burning mouth syndrome (n=20) Mean age: 46.9 (4.95) years Duration of pain: 14.45 (6-36) years	At 2 weeks (post-intervention): • Quality of life • Pain reduction	Burning mouth syndrome defined as burning sensation in the oral cavity for at least 4 months without any identified causes.

Study	Intervention and comparison	Population	Outcomes	Comments
Armagan 2006[31]	10 days interventions **Intervention 1: Laser therapy (n=16)** **Number of sessions:** 10 (over 10 days) **Duration:** 1 minute per tender point **Delivered by:** Physician **Details**: 830nm wavelength, 50mW power, laser diameter 1mm, 1 minute per tender point at 2 joules per tender point. **Intervention 2: Sham laser therapy (n=16)** **Details:** Identical treatment but laser not turned on.	Fibromyalgia (n=32) Mean age: 38.25 (5.36) years Duration of pain: 5.8 (3.2) years All women	At 10 days (post-intervention) and 6 months (follow up, including 10 day intervention): • Quality of life	
Bardellini 2019[37]	10 weeks interventions **Intervention 1: Laser therapy (n=45)** **Number of sessions:** 10 (over 10 weeks) **Duration:** unclear **Delivered by:** Dentist **Details:** K Laser Cube 3® irradiated the most painful areas in the oral cavity, with discontinuous combined wavelengths between 660-970 nm, medium power 3.2 W (6.4 W pulsed at 50%), treatment time 3'51", frequency 1-20000Hz, spot size 1cm². **Intervention 2:** Sham laser therapy (n=45) **Details:** The device was turned on but the hand piece did not work.	Burning mouth syndrome (n=90) Mean age: laser group: 60.31 (9.78) years Duration of pain: inclusion criteria specified >6 months, mean duration not reported All female	At 10 weeks (post-intervention) and 14 weeks (1 month follow up): • Quality of life	
Boyer 2014[53]	10 week interventions **Intervention 1: TMS (n=19)** **Number of sessions:** 14 (over 10 weeks) **Duration:** Not reported	Fibromyalgia (n=38) Mean age: 48.5 (10.5) years	At 10 weeks (post-intervention): • Quality of life • Psychological distress	Inclusion criteria: score of at least 4 on the BPI average pain intensity scale

Study	Intervention and comparison	Population	Outcomes	Comments
	Delivered by: Not reported **Details:** No further details available **Intervention 2: Sham TMS (n=19)** **Details:** Identical treatment but a sham coil used that emitted a similar sound to the active coil	Duration of pain: 3.7 (4.2) years		
Brietzke 2019 [54]	3 month interventions **Intervention 1: TDCS (n=10)** **Number of sessions:** 60 sessions over 12 weeks **Duration: approx.** 30 minutes **Delivered by:** Self-administered **Details:** 2mA current applied through electrodes over the left dorsolateral prefrontal cortex (DLPFC) attached to cap (caps individually fitted to each participant). **Intervention 2: Sham TDCS (n=10)** **Details:** Identical treatment but no electrical stimulation	Fibromyalgia (n=40) Mean age 49.1 years Duration of pain: 6.2 years	At 3 months (post-intervention) • Psychological distress • Sleep	Intervention self-administered at home. The electrode position was accurate for the subjects. To avoid incorrect placement of the electrodes, the anode was painted red and cathode black (although equipment was already set up – participant could not change any part of it).
Carretero 2009[61]	4 week interventions **Intervention 1: TMS (n=14)** **Number of sessions:** 20 sessions over 4 weeks **Duration: approx.** 30 minutes **Delivered by:** Not reported **Details:** Butterfly coil used, 20 trains at 110% of motor threshold for 60s at 1Hz and a 45s interval between trains. Stimulation area right dorsolateral prefrontal area (total of 1,200 pulses per session) **Intervention 2: Sham TMS (n=12)**	Fibromyalgia (n=26) Mean age: 51.2 (5.3) years Duration of pain not stated	At 3 months (follow up, including 4 week intervention): • Pain reduction	

Study	Intervention and comparison	Population	Outcomes	Comments
	Details: Identical treatment but coil placed perpendicular to the cranium (the magnetic field did not significantly penetrate the brain)			
Chow 2004[77]	7 week interventions **Intervention 1: Laser therapy (n=10)** **Number of sessions: 7** (over 7 weeks) **Duration:** 30 minutes **Delivered by:** Not reported **Details:** 830nm, 15mm laser length and 3mm width, 300mW power, applied 30s per point or until area became less tender **Intervention 2: Sham laser therapy (n=10)** **Details:** Identical treatment but laser did not emit a beam	Chronic neck pain (n=20) Mean age: 57.7(10.9) years Duration of pain: 13.3 years (SE 2.48)	At 3 months (follow up, including 7 week intervention): • Quality of life • Pain reduction	Participants that had previously received laser therapy were excluded (other than laser acupuncture). People with work related or third party injuries in which litigation or compensation were still current were excluded.
Chow 2006[78]	7 week interventions **Intervention 1: Laser therapy (n=45)** **Number of sessions:** 7 (over 7 weeks) **Duration:** 30 minutes **Delivered by:** Not reported **Details:** 830nm wavelength, 300mW, each tender point treated for 30 seconds, up to 50 points treated **Intervention 2: Sham laser (n=45)** **Details:** Identical treatment but device did not emit laser (although did emit sound)	Chronic neck pain (n=90) Mean age: 56 (12.8) years Duration of pain: 15 (12.6) years	At 3 months (follow up, including 7 week intervention): • Quality of life • Pain reduction • Discontinuation	People with work related or third party injuries in which litigation or compensation were still current were excluded.
da Cunha 2008[92]	4 week interventions **Intervention 1: Laser therapy (n=20)** **Number of sessions:** 4 (over 4 weeks)	Temporomandibular disorder (n=40)	At 4 weeks (post-intervention) • Pain reduction	Temporomandibular disorder diagnosed based on complete clinical examination, including patient's

Study	Intervention and comparison	Population	Outcomes	Comments
	Duration: Not reported (each area irradiated for 20s) **Delivered by:** Not reported **Details:** 830nm wavelength, 500mW output, each area irradiated for 20s **Intervention 2: Sham laser (n=20)** **Details:** Identical treatment but without energy output	Mean age: 43.3 years Duration of pain: Not stated		history, at the Center of Occlusion and Temporomandibular Disorder of the Dental School of Sao Paulo State University (UNESP).
Dailey 2019 [94]	4 week interventions **Intervention 1: TENS (n=103)** **Number of sessions:** Not reported **Duration:** at least 2 hours/day during activity **Delivered by:** self-administered (first application delivered in clinic) **Details:** EMPI-Select TENS (DJO Global, Vista, CA) delivered through butterfly electrodes placed at the cervicothoracic junction and lower back. Active-TENS parameters were asymmetrical, biphasic waveform with a modulating frequency (2-125 Hz), pulse duration 200µ sec, and highest tolerable stimulation intensity. Active-TENS was sent home with participants with an instruction manual developed by study personnel. **Intervention 2: sham TENS (n=99)** **Details:** delivered current for 45s ramping down to 0 in the last 15s and the appearance was identical to the active unit. **Intervention 3: Usual care (n=99)** **Details:** used a mock-TENS during visits to blind Outcome-Assessors with electrodes that were attached to a TENS unit that provided no current intensity.	Fibromyalgia (n=301) Mean age: 46.8 (13.06) years Duration of pain median (range): 7 (2-15) years All female	At 4 weeks (post intervention): • Quality of life • Pain reduction • Physical function • Psychological distress • Pain interference • Pain self-efficacy	All participants continued current treatments prescribed by their health care provider and were asked not to change medications during the study.

Study	Intervention and comparison	Population	Outcomes	Comments
Dall'Agnol 2014[96]	10 day interventions **Intervention 1: TMS (n=12)** **Number of sessions:** 10 (over 10 days) **Duration:** Not reported **Delivered by:** Not reported **Details:** Figure 8 coil placed over left motor cortex, trains consisted of 16 series of 10-s pulses at 10Hz, interval of 26s between trains. Intensity was 80% of resting motor threshold **Intervention 2: sham TMS (n=12)** **Details:** Identical treatment but inactive sham coil used (identical sounds and sensations but no brain stimulation)	Myofascial pain (n=24) Mean age: 45.43 (12.86) years Duration of pain: Not stated All women	At 3 months (follow up, including 10 day intervention): • Pain reduction	Number of sessions stated to be 10, but duration of study not specified. Myofascial pain defined as reduced quality of life due to regional pain, decreased range of motion, stiffness in muscles, presence of trigger points, taut bands, tender points, palpable nodules and pain. Must have score of more than 4 on the neuropathic pain diagnostic questionnaire.
Del Vecchio 2019 [101]	1 week interventions **Laser therapy (n=30)** **Number of sessions:** 14 (over 7 days; delivered at home) **Duration:** 1 week **Delivered by:** Self-administered (first application delivered in clinic) **Details:** Laser with 808nm wavelength, 5J/min, 250mW and 15KHz for 8 minutes, for a total of 40J applied directly to each painful area. **Sham laser therapy (n=30)** **Details:** identical device with beam and sound but devoid of therapeutic diode source.	Temporomandibular joint disorder-related pain (n=60) Mean age: 42.55 (14.842) years Duration of pain not specified (minimum duration 6 months)	At 1 week (post-intervention): • Pain reduction	The inclusion criteria were: presence of pain in the joint area and/or radiating to the face, jaw, or neck for at least six months; reduced mouth opening or jaw locks; painful clicking, popping or grating when opening or closing the mouth; occlusal changes; no muscle

Study	Intervention and comparison	Population	Outcomes	Comments
				tenderness at palpation; and no drug consumption for at least three weeks before treatment. The disorder was diagnosed by clinical and radiological examinations and according to the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) Axis I and Axis II
Esenyel 2000[117]	10 day interventions **Intervention 1: Ultrasound (n=36)** **Number of sessions:** 10 (over 10 days) **Duration:** 6 mins per trigger point **Delivered by:** Not reported **Details:** 1.5Wcm^2 applied to each trigger point for 6 minutes. Neck exercises also advised **Intervention 2: Usual care (n=40)** **Details:** Usual care as well as advice on neck stretching exercises	Myofascial pain (n=76) Mean age: 30 (7.7) years Duration of pain: ranged 6 months to 7 years	At 3 months (follow up, including 10 day intervention): • Pain reduction	Myofascial pain followed Travel and Simons criteria for active myofascial trigger points in the upper trapezius muscles
Fagerlund 2015[120]	5 day interventions **Intervention 1: TDCS (n=25)** **Number of sessions:** 5 (over 5 days) **Duration:** 20 minutes	Fibromyalgia (n=50) Mean age: 48.6 (9.4) years	At 4 weeks (follow up, including 5 day intervention): • Quality of life • Pain reduction	

Study	Intervention and comparison	Population	Outcomes	Comments
	Delivered by: Not reported **Details:** Intensity 2mA, anode placed on C3 and cathode placed on contralateral supraorbital area **Intervention 2: Sham TDCS (n=25)** **Details:** Identical treatment but stimulation faded in for 30s, then terminated by 5s fade out (to mimic skin sensation of active treatment with insufficient duration to induce cortical excitability)	Duration of pain: 18.1 (9) years	• Psychological distress	
Fregni 2006[129]	1 week interventions *Note: interventions 1 and 2 pooled in the analysis.* **Intervention 1: TDCS (DLPFC) (n=11)** **Number of sessions:** 5 (over 5 days) **Duration:** 20mins **Delivered by:** Not reported **Details:** Current transferred by pair of saline soaked sponge electrodes, max output 10mA, anode on left DLPFC brain area, constant current of 2mA applied for 20mins **Intervention 2: TDCS (motor cortex [M1]) (n=11)** **Number of sessions:** 5 (over 5 days) **Duration:** 20mins **Delivered by:** Not reported **Details:** Current transferred by pair of saline soaked sponge electrodes, max output 10mA, anode on primary motor cortex brain area, constant current of 2mA applied for 20mins **Intervention 3: Sham TDCS (n=10)** **Details:** Identical treatment but with sham stimulation of the primary motor cortex (stimulator turned off after	Fibromyalgia (n=32) Mean age: 53.2 (8.97) years Duration of pain: 8.4 (9.3) years All women	At 3 weeks (follow up, including 1 week intervention): • Psychological distress	Inclusion criteria: score of at least 4 on the VAS and at least 30 on the total tender point score.

Study	Intervention and comparison	Population	Outcomes	Comments
	30s to mimic sensation but no current received after this)			
Gokyildiz 2012[137]	12 week interventions **Intervention 1: PENS (n=13)** **Number of sessions:** 12 (over 3 months) **Duration:** 30mins **Delivered by:** Not reported **Details:** Percutaneous tibial nerve stimulation, applied using a needle set and stimulator with 9-volt batteries and current between 0.5-10mA, 20Hz frequency. Needle inserted 3-4cm above inner malleolus and electrode placed on inner side of the heel. Current adjusted based on tolerance **Intervention 2: Usual care (n=13)** **Details:** Routine usual care, no further details	Chronic pelvic pain (n=26) Mean age: Not reported Duration of pain: Not reported (minimum duration 6 months)	At 3 months (post-intervention): • Quality of life • Pain reduction	Score of at least 5 on VAS. Cessation of analgesics at least 2 weeks before treatment, and physiotherapy or electrotherapy at least 3 months before treatment.
Gur 2002[147]	2 week interventions **Intervention 1: Laser therapy (n=25)** **Number of sessions:** 14 (over 2 weeks) **Duration:** Not reported (3 mins per tender point) **Delivered by:** Physical therapists **Details:** 904nm wavelength, 20W max per pulse, 200ns max pulse duration, 2.8Hz pulse frequency, 11.2mW average power, 3 mins at each tender point **Intervention 2: Sham laser therapy (n=25)** **Details:** Identical treatment but no laser beam emitted	Fibromyalgia (n=50) Mean age: 29.44 (6.6) years Duration of pain: 4.74 (3.98) years	At 2 weeks (post-intervention): • Pain reduction	All participants discontinued medications at least 1 month prior to treatment
Jales 2015[167]	10 week interventions **Intervention 1: TDCS (n=10)**	Fibromyalgia (n=20)	At 10 weeks (post-intervention): • Quality of life	

Study	Intervention and comparison	Population	Outcomes	Comments
	Number of sessions: 10 (over 10 weeks) **Duration:** 20 minutes **Delivered by:** Not reported **Details:** 2 electrodes placed on scalp, 1mA impulse applied (anode over m1, cathode over contralateral supraorbital region). Applied for 20 mins **Intervention 2: Sham TDCS (n=10)** **Details:** Identical treatment but device not turned on	Mean age: 46.4 (10.615) years Duration of pain: Not reported All women	• Pain reduction	
Kabay 2009[176]	12 week interventions **Intervention 1: PENS (n=45)** **Number of sessions:** 12 (over 3 months) **Duration:** 30 mins **Delivered by:** Not reported **Details:** Percutaneous posterior tibial nerve stimulation, needle inserted 5cm from medial malleolus and electrode placed on same leg. Electrical stimulation applied with 200us pulses, rate of Hz, intensity level just below motor threshold. Amplitude set at maximum tolerable (using 1.5x threshold for evoking plantar flexion) **Intervention 2: Sham PENS (n=44)** **Details:** Identical treatment but electrical stimulation not applied.	Pelvic pain (n=89) Mean age: 37.7(7.4) years Duration of pain: 4.5 (6.1) years	At 3 months (post-intervention): • Quality of life • Pain reduction	Diagnosis of category IIIB CP/CPPS
Khedr 2017[185]	2 week interventions **Intervention 1: TDCS (n=20)** **Number of sessions:** 10 (over 2 weeks) **Duration:** 20mins **Delivered by:** Not reported	Fibromyalgia (n=40) Mean age: 32.3 (10.9) years Duration of pain: 6.1 (2.5) years	At 8 weeks (follow up, including 2 week intervention): • Pain reduction • Psychological distress	Score of at least 4 on VAS pain scale

Study	Intervention and comparison	Population	Outcomes	Comments
	Details: 2mA, anodal electrode on left M1 over C3, reference electrode over contralateral arm. **Intervention 2: Sham TDCS (n=20)** **Details:** Identical treatment but current applied for 30s only at the beginning and at the end of the session.			
Lee 2012[205]	10 day interventions Note: intervention 1 and 2 pooled in the analysis **Intervention 1: TMS (low frequency) (n=7)** **Number of sessions:** 10 (over 10 days) **Duration:** Not reported **Delivered by:** Physiatrist **Details:** Figure 8 coil, applied to right M1 (at the DLPFC), 1Hz, 110% intensity of resting motor threshold, 800 stimuli of each train and 2 trains with 60s of inter-train interval and a total of 1600 stimuli per session. **Intervention 2: TMS (high frequency) (n=8)** **Details:** Identical treatment to intervention 2 but 80% of resting motor threshold, 2000 stimuli per session. **Intervention 3: Sham TMS (n=7)** **Details:** Identical treatment but coil angle was 90% perpendicular to skull (magnetic field did not penetrate the brain).	Fibromyalgia (n=22) Mean age: 47.2(6.2) years Duration of pain: 44.7(10.3) years All women	At 6 weeks (follow up, including 10 day intervention): • Quality of life • Pain reduction • Psychological distress • Discontinuation	Inclusion criteria: pain for at least 24 months
Mhalla 2011[241]	21 week interventions **Intervention 1: TMS (n=20)** **Number of sessions:** 14 (over 21 weeks) **Duration:** Not reported **Delivered by:** Not reported	Fibromyalgia (n=40) Mean age: 50.2 (10.8) years	At 25 weeks (follow up, including 21 week intervention): • Quality of life • Psychological distress • Pain interference	Score of at least 4 on BPI pain scale.

Study	Intervention and comparison	Population	Outcomes	Comments
	Details: figure 8 coil, positioned to induce current in the anterior posterior direction, 15 series of 10s pulses, frequency 10Hz, interval of 50s between each train, total of 1500 pulses per session (stimulation intensity 80% of resting motor threshold) **Intervention 2: Sham TMS (n=20)** **Details:** Identical treatment but sham coil used	Duration of pain: 13.55 (12.4) years All women		
Murina 2008[250]	10 week interventions **Intervention 1: TENS (n=20)** **Number of sessions:** 20 (over 10 weeks) **Duration:** 15-30 mins **Delivered by:** Not reported **Details:** Electrical stimulation via vaginal probe 20mm in diameter, 110mm in length. Frequencies of 10 and 50Hz at 15min intervals. **Intervention 2: Sham TENS (n=20)** **Details:** Identical treatment but nonactive stimulation (2Hz, pulse duration 2ms followed by 15min pause).	Vestibulodynia (n=40) Mean age: 28 (21-44) years Duration of pain: 15 month (range 7-48 months) All women	At 10 weeks (post-intervention): • Pain reduction • Discontinuation	
Panton 2013[274]	4 week interventions **Intervention 1: Laser therapy (n=23)** **Number of sessions:** 8 (over 4 weeks) **Duration:** 15 mins **Delivered by:** Not reported **Details:** Laser applied to 7 tender points with dual wavelength laser (20% 810nm and 80% 980nm), heat also applied via warm air, each point treated for 60s for total of 600J per point **Intervention 2: Sham laser (n=18)**	Fibromyalgia (n=41) Mean age: 53 (11.5) years Duration of pain: 10.5 (7.5) years All women	At 4 weeks (post-intervention): • Quality of life • Pain reduction • Discontinuation	Participants received $100 for participating in the study.

Study	Intervention and comparison	Population	Outcomes	Comments
	Details: Identical treatment but laser not turned on			
Rohlig 2011[289]	3 week interventions **Intervention 1: Laser therapy (n=20)** **Number of sessions:** 10 (over 3 weeks) **Duration:** Not reported (10s per tender point) **Delivered by:** Not reported **Details:** 820nm wavelength, beam diameter 6mm, 8J/cm2 to each tender point **Intervention 2: Sham laser therapy (n=20)** **Details:** Identical treatment but laser not turned on	Temporomandibular disorder (n=40) Mean age: 42.5 (2.3) years Duration of pain: 10.75 (2.9) years	At 3 weeks (post-intervention): • Pain reduction	Presence of signs and symptoms of TMD of myogenic origin according to the research diagnostic criteria for TMD.
Short 2011[314]	2 week interventions **Intervention 1: TMS (n=10)** **Number of sessions:** 10 (over 2 weeks) **Duration:** 20 mins **Delivered by:** Not reported **Details:** Applied to left prefrontal cortex, 10Hz, 5s train duration, intensity 120% resting motor threshold **Intervention 2: Sham TMS (n=10)** **Details:** Identical treatment but sham TMS coil used	Fibromyalgia (n=20) Mean age: 53 (13.53) years Duration of pain: 11.1 (10.36) years	At 4 weeks (follow up, including 2 week intervention): • Quality of life • Pain reduction • Physical function • Psychological distress	
Spanemberg 2015[325]	3 week interventions *Note: intervention 1 and 2 pooled in analysis* **Intervention 1: Laser therapy (infrared) (n=20)** **Number of sessions:** 9 (over 3 weeks) **Duration:** M50s per point **Delivered by:** Not reported	Burning mouth syndrome (n=58) Mean age: 61.9 (8.76) years	At 8 weeks (follow up, including 3 week intervention): • Quality of life • Pain reduction	Burning or pain in the oral mucosa for at least 6 months with clinically normal mucosa.

Study	Intervention and comparison	Population	Outcomes	Comments
	Details: 830nm wavelength, 100mW output, continuous emissions, 5J energy per point, 50s per point. **Intervention 2: Laser therapy (red laser) (n=19)** **Details:** Identical treatment but red laser at 685nm wavelength, 2J per point, 35mQ output power **Intervention 3: Sham laser therapy (n=19)** **Details:** Identical treatment but sham laser	Duration of pain: Not reported (minimum 6 months)		
Sugaya 2016[329]	2 week interventions **Intervention 1: Laser therapy (n=15)** **Number of sessions:** 4 (over 2 weeks) **Duration:** Not reported **Delivered by:** Not reported **Details:** 6J/cm2, applied to entire area affected by burning sensation. No further details. **Intervention 2: Sham laser therapy (n=15)** **Details:** Identical treatment but no laser energy delivered (machine still appeared active)	Burning mouth syndrome (n=30) Mean age: 59.7(29-83) years Duration of pain: 31.7 months (range 6 to 192)	At 3 months and 16 weeks (follow up, including 2 week intervention): • Pain reduction	Exclusion criteria: Clinical alterations in the oral mucosa potentially associated with the burning symptoms
Tekin 2014[339]	10 day interventions **Intervention 1: TMS (n=27)** **Number of sessions:** 10 (over 10 days) **Duration:** Not reported **Delivered by:** Psychiatry physician **Details:** Figure 8 coil, 30 sequential series each for 5s at 10Hz, at 100% of motor threshold, 12s interval between series	Fibromyalgia (n=52) Mean age: 44.4 (8.1) years Duration of pain: 12.1 (6.47) years	At 10 weeks (post-intervention): • Quality of life • Pain reduction • Psychological distress • Discontinuation	No analgesic use for at least 1 month prior to treatment

Study	Intervention and comparison	Population	Outcomes	Comments
	Intervention 2: Sham TMS (n=25) **Details:** Identical treatment but placebo sham coil used.			
Umezaki 2016[345]	10 day interventions **Intervention 1: TMS (n=14)** **Number of sessions:** 10 (over 10 days) **Duration:** Not reported **Delivered by:** Not reported **Details:** Figure 8 coil, positioned around primary motor cortex, 10Hz frequency, 5s pulse train duration, intensity 110% of resting motor threshold, total 30,000 pulses **Intervention 2: Sham TMS (n=12)** **Details:** Identical treatment but coil was shielded so actual stimulation did not occur.	Burning mouth syndrome (n=26) Mean age: 63.85 (9.56) years Duration of pain: 63.42 (65.51) years	At 8 weeks (follow up, including 10 day intervention): • Pain reduction • Discontinuation (at 1 week)	Diagnosis of BMS confirmed by (1) daily and deep bilateral burning sensation of the oral mucosa, burning sensation for at least 4-56 months, constant intensity or increasing intensity during the day, no worsening but possible improvement on eating or drinking, no interference with sleep and normal appearing oral mucosa.
Valenzuela 2017[346]	4 week interventions *Note: intervention 1 and 2 pooled in the analysis* **Intervention 1: Laser therapy (low intensity) (n=16)** **Number of sessions:** 4 (over 4 weeks) **Duration:** Not reported **Delivered by:** Not reported **Details:** 815nm wavelength, 1W output, 4s per point, 4J, applied intra-orally and spot sizes of 0.03cm^3. **Intervention 2: Laser therapy (high intensity) (n=16)** **Details:** Identical treatment but 6J energy over 6s **Intervention 3: Sham laser therapy (n=12)**	Burning mouth syndrome (n=44) Mean age: 65.5 (10.6) years Duration of pain: Not reported	At 4 weeks (post-intervention): • Quality of life • Pain reduction • Psychological distress	Burning mouth syndrome diagnosis according to international classification of headaches

Study	Intervention and comparison	Population	Outcomes	Comments
	Details: Identical treatment but laser turned off			
Venancio 2005[354]	3 week interventions **Intervention 1: Laser therapy (n=15)** **Number of sessions:** 6 (over 3 weeks) **Duration:** Not reported **Delivered by:** Not reported **Details:** 780nm wavelength, 30mW output, 10s duration at each point **Intervention 2: Sham laser therapy (n=15)** **Details:** Identical treatment but laser device not turned on	Temporomandibular disorder (n=30) Mean age: 36.25 (13-63) years Duration of pain: 44.8 months (range 6-120 months)	At 8 weeks (follow up, including 3 week intervention): • Pain reduction	TMD diagnosis according to criteria of the American Academy of Orofacial pain
Yagci 2014[375]	2 week interventions **Intervention 1: TMS (n=14)** **Number of sessions:** 10 (over 2 weeks) **Duration:** Not reported **Delivered by:** Not reported **Details:** Stimulation of motor cortex area, applied stimulation at 90% of motor threshold for 60s at 1Hz and 45s intervals between trains (1200 pulses in total each session) **Intervention 2: Sham TMS (n=14)** **Details:** Identical treatment but sham coil used	Fibromyalgia (n=28) Mean age: 44.9(8.6) years Duration of pain: 53.5 (29.8) months All women	At 3 months (follow up, including 2 week intervention): • Quality of life • Pain reduction • Psychological distress	

1 See appendix D for full evidence tables.

1.4.4 Quality assessment of clinical studies included in the evidence review

2 **Table 3: Clinical evidence summary: Laser therapy versus sham laser therapy**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Laser therapy versus sham laser therapy (95% CI)
Quality of life at ≤3 months (Oral health impact profile, FIQ, high is poor outcome, final values)	276 (6 studies) 2 weeks-3 months	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, inconsistency, imprecision		-	The mean quality of life score in the intervention groups was 0.68 standard deviations lower (1.1 to 0.25 lower)
Quality of life at ≤3 months (SF-36 physical component summary score, 0-100, high is good outcome, change scores)	110 (2 studies) 3 months	⊕⊕⊕⊖ MODERATE1 due to imprecision		The mean quality of life change score in the control groups was 1.26	The mean quality of life score in the intervention groups was 2.09 higher (0.91 lower to 5.09 higher)
Quality of life at ≤3 months (SF-36 mental component summary score, 0-100, high is good outcome, change scores)	110 (2 studies) 3 months	⊕⊕⊖⊖ LOW1,2 due to inconsistency, imprecision		The mean quality of life change score in the control groups was 2.7	The mean quality of life score in the intervention groups was 0.74 lower (5.35 lower to 3.87 higher)
Quality of life at >3 months (FIQ, Oral health impact profile, high is poor outcome, final values)	117 (2 studies) 14-24 weeks	⊕⊕⊖⊖ LOW1,3 due to risk of bias, imprecision		-	The mean quality of life score in the intervention groups was 0.78 standard deviations lower (1.16 to 0.4 lower)
Pain reduction at ≤3 months (VAS, NRS, FIQ pain scale, high is poor outcome, 0-10, final values and change scores)	558 (13 studies) 1 week-3 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, inconsistency, imprecision		The mean pain reduction score in the control groups was 4.97	The mean pain reduction score in the intervention groups was 1.42 lower (2.12 to 0.73 lower)
Pain reduction at >3 months (VAS, high is poor outcome, 0-10, final values)	71 (2 studies) 14-16 weeks	⊕⊕⊕⊖ MODERATE1 due to imprecision		The mean pain reduction score in the control groups was 2.8	The mean pain reduction score in the intervention groups was 0.6 lower (0.91 to 0.3 lower)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Laser therapy versus sham laser therapy (95% CI)
Psychological distress at ≤3 months (Hospital anxiety and depression rating scale, anxiety subscale, 0-21, high is poor outcome, final values)	44 (1 study) 4 weeks	⨁⨁⨀⨀ LOW1,3 due to risk of bias, imprecision		The mean psychological distress score in the control groups was 10.33	The mean psychological score in the intervention groups was 0.83 higher (1.52 lower to 3.18 higher)
Psychological distress at ≤3 months (Hospital anxiety and depression rating scale, depression subscale, 0-21, high is poor outcome, final values)	48 (1 study) 4 weeks	⨁⨁⨀⨀ LOW1,3 due to risk of bias, imprecision		The mean psychological distress score in the control groups was 7.25	The mean psychological distress score in the intervention groups was 1.29 higher (1.39 lower to 3.96 higher)
Discontinuation at ≤3 months	90 (1 study) 3 months	⨁⨁⨁⨀ LOW1 due to imprecision	RR 0.67 (0.12 to 3.8)	67 per 1000	22 fewer per 1000 (from 59 fewer to 188 more)

1 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
2 Downgraded for heterogeneity, unexplained by subgroup analysis
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

1 **Table 4: Clinical evidence summary: TMS versus sham TMS**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with TMS versus sham TMS (95% CI)
Quality of life at ≤3 months (SF-36 physical summary score, 0-100, high is good outcome, change scores)	29 (1 study) 10 weeks	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, imprecision		The mean quality of life change score in the control groups was 0.4	The mean quality of life score in the intervention groups was 1 higher (4.12 lower to 6.12 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with TMS versus sham TMS (95% CI)
Quality of life at ≤3 months (SF-36 mental summary score, 0-100, high is good outcome, change scores)	29 (1 study) 10 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean quality of life change score in the control groups was -1.6	The mean quality of score in the intervention groups was 6.6 higher (1.26 to 11.94 higher)
Quality of life at ≤3 months (WHOQOL-BREF physical domain, 4-20, high is good outcome, final values)	51 (1 study) 2 weeks	⊕⊕⊕⊕ HIGH		The mean quality of life score in the control groups was 11.33	The mean quality of score in the intervention groups was 3.27 higher (1.79 to 4.75 higher)
Quality of life at ≤3 months (WHOQOL-BREF psychological domain, 4-20, high is good outcome, final values)	51 (1 study) 2 weeks	⊕⊕⊕⊖ MODERATE2 due to imprecision		The mean quality of score in the control groups was 12.71	The mean quality of score in the intervention groups was 1.18 higher (0.18 lower to 2.54 higher)
Quality of life at ≤3 months (FIQ, 0-100, high is poor outcome, final values)	60 (3 studies) 4 weeks-3 months	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean quality of life score in the control groups was 49.92	The mean score in the intervention groups was 8.69 lower (18.83 lower to 1.46 higher)
Quality of life at >3 months (FIQ, 0-100, high is poor outcome, final values)	30 (1 study) 25 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean quality of life score in the control groups was 63.3	The mean quality of life score in the intervention groups was 7.3 lower (19.04 lower to 4.44 higher)
Pain reduction at ≤3 months (VAS, McGill Pain questionnaire, 0-10, high is poor outcome, final values)	181 (7 studies) 2 weeks-3 months	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, inconsistency, imprecision		The mean pain reduction score in the control groups was 5.68	The mean pain reduction score in the intervention groups was 1.17 lower (2.1 to 0.24 lower)
Physical function at ≤3 months (BPI functional impairment subscale, 0-10, high is poor outcome, final values)	20 (1 study) 4 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean physical function score in the control groups was 3.79	The mean physical function score in the intervention groups was 0.19 lower (2.34 lower to 1.96 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with TMS versus sham TMS (95% CI)
Psychological distress at ≤3 months (Beck depression inventory, 0-61, high is poor outcome, final values and change scores)	44 (2 studies) 6-10 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		-	The mean psychological score in the intervention groups was 1.59 lower (4.13 lower to 0.94 higher)
Psychological distress at ≤3 months (Hamilton depression rating scale, MADRS, BDI, high is poor outcome, final values)	96 (3 studies) 2 weeks-3 months	⊕⊕⊕⊖ MODERATE1 due to risk of bias		-	The mean psychological distress score in the intervention groups was 0.01 standard deviations higher (0.39 lower to 0.41 higher)
Psychological distress at ≤3 months (HADS anxiety, 0-21, high is poor outcome, change scores)	29 (1 study) 10 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean psychological distress change score in the control groups was 0.5	The mean psychological distress score in the intervention groups was 0.1 lower (1.6 lower to 1.4 higher)
Psychological distress at >3 months (HADS anxiety, 0-21, high is poor outcome, change scores)	30 (1 study) 25 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean psychological distress change score in the control groups was 9.4	The mean psychological score in the intervention groups was 0.2 lower (4 lower to 3.6 higher)
Psychological distress at >3 months (HADS depression, 0-21, high is poor outcome, change scores)	30 (1 study) 25 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean psychological distress change score in the control groups was 7.4	The mean psychological score in the intervention groups was 1.2 higher (1.92 lower to 4.32 higher)
Pain interference at >3 months (BPI pain interference, 0-10, high is poor outcome, final values)	30 (1 study) 25 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean pain interference score in the control groups was 6	The mean pain interference score in the intervention groups was 1.9 lower (3.05 to 0.75 lower)
Discontinuation at ≤3 months	141 (4 studies) 2-6 weeks	⊕⊕⊖⊖ LOW2 due to imprecision	RD 0.03 (-0.06 to 0.12)	20 per 1000	30 more per 1000 (from 60 fewer to 120 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with TMS versus sham TMS (95% CI)
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 1 MID or by 2 increments if the confidence interval crossed both MIDs. 3 Downgraded for heterogeneity, unexplained by subgroup analysis					

Table 5: Clinical evidence summary: 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 Control	Risk difference with TDCS versus sham TDCS (95% CI)
Quality of life at ≤3 months (SF-36 mental summary score, 0-100, high is good outcome, final values)	48 (1 study) 4 weeks	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean quality of life in the control groups was 45.4	The mean quality of life score in the intervention groups was 2.8 higher (4.72 lower to 10.32 higher)
Quality of life at ≤3 months (SF-36 physical summary score, 0-100, high is good outcome, final values)	48 (1 study) 4 weeks	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean quality of life in the control groups was 35.92	The mean quality of life score in the intervention groups was 1.14 lower (5.92 lower to 3.64 higher)
Quality of life at ≤3 months (SF-36 physical function subscale, 0-100, high is good outcome, final values)	20 (1 study) 10 weeks	⨁⨁⨁⊖ MODERATE1 due to risk of bias		The mean quality of life score in the control groups was 38	The mean quality of score in the intervention groups was 30.5 higher (12.47 to 48.53 higher)
Quality of life at ≤3 months (SF-36 physical role subscale, 0-100, high is good outcome, final values)	20 (1 study) 10 weeks	⨁⊖⊖⊖ VERY LOW1,2 due to risk of		The mean quality of score in the control groups was 47.5	The mean quality of life score in the intervention groups was 27.5 higher (4.71 lower to 59.71 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with TDCS versus sham TDCS (95% CI)
		bias, imprecision			
Quality of life at ≤3 months (SF-36 bodily pain subscale, 0-100, high is good outcome, final values)	20 (1 study) 10 weeks	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean quality of life score in the control groups was 50	The mean quality of life score in the intervention groups was 7 lower (25.49 lower to 11.49 higher)
Quality of life at ≤3 months (SF-36 general health subscale, 0-100, high is good outcome, final values)	20 (1 study) 10 weeks	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean quality of life score in the control groups was 63.5	The mean quality of life score in the intervention groups was 5.5 lower (14.54 lower to 3.54 higher)
Quality of life at ≤3 months (SF-36 vitality subscale, 0-100, high is good outcome, final values)	20 (1 study) 10 weeks	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean quality of life score in the control groups was 58	The mean quality of life score in the intervention groups was 4.5 lower (12.92 lower to 3.92 higher)
Quality of life at ≤3 months (SF-36 general aspects subscale, 0-100, high is good outcome, final values)	20 (1 study) 10 weeks	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean quality of life score in the control groups was 50	The mean quality of life score in the intervention groups was 2.5 lower (16.55 lower to 11.55 higher)
Quality of life at ≤3 months (SF-36 emotional role subscale, 0-100, high is good outcome, final values)	20 (1 study) 10 weeks	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean quality of score in the control groups was 60	The mean quality of life score in the intervention groups was 20 higher (15.04 lower to 55.04 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with TDCS versus sham TDCS (95% CI)
Quality of life at ≤3 months (SF-36 mental health subscale, 0-100, high is good outcome, final values)	20 (1 study) 10 weeks	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean quality of score in the control groups was 54	The mean quality of life score in the intervention groups was 4.4 higher (5.82 lower to 14.62 higher)
Pain reduction at ≤3 months (NRS, VAS, 0-10, high is poor outcome, final values)	104 (3 studies) 4-10 weeks	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, inconsistency, imprecision		The mean pain reduction score in the control groups was 6.04	The mean pain reduction score in the intervention groups was 2.12 lower (3.82 to 0.43 lower)
Psychological distress at ≤3 months (Hospital anxiety and depression scale, HAM-A, anxiety subscales, high is poor outcome, final values)	84 (2 studies) 4-8 weeks	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, inconsistency, imprecision		-	The mean psychological distress score in the intervention groups was 0.55 standard deviations lower (1.49 lower to 0.39 higher)
Psychological distress at ≤3 months (Hospital anxiety and depression scale, BDI, HAM-D, depression subscales, high is poor outcome, final values)	136 (4 studies) 3-12 weeks	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, imprecision, inconsistency		-	The mean psychological distress score in the intervention groups was 0.39 standard deviations lower (1.06 lower to 0.28 higher)
Sleep at ≤3 months (PSQI, scale range not reported, high is poor outcome, final values)	20 (1 study) 12 weeks	⊕⊕⊕⊖ MODERATE2 due to risk of bias		The mean sleep in the control groups was 16.7	The mean psychological distress score in the intervention groups was 8.8 lower (13.96 to 3.64 lower)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with TDCS versus sham TDCS (95% CI)

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 1 MID or by 2 increments if the confidence interval crossed both MIDs.
3 Downgraded for heterogeneity, unexplained by subgroup analysis

1 **Table 6: Clinical evidence summary: TENS versus sham TENS**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with TENS versus sham TENS (95% CI)
Quality of life at ≤3 months (SF36 physical component T scores, high is good outcome, change scores)	202 (1 study) 4 weeks	⊕⊕⊕⊖ MODERATE1 due to risk of bias		The mean change in quality of life score in the control groups was 1.2	The mean change in quality of life score in the intervention groups was 1.2 higher (0.7 lower to 3.1 higher)
Quality of life at ≤3 months (SF36 mental component T scores, high is good outcome, change scores)	202 (1 study) 4 weeks	⊕⊕⊕⊖ MODERATE1 due to risk of bias		The mean change in quality of life score in the control groups was 1.2	The mean change in quality of life score in the intervention groups was 1.1 higher (1.9 lower to 4.1 higher)
Pain reduction at ≤3 months (VAS, BPI intensity, 0-10, high is poor outcome, final values and change scores)	242 (2 studies) 4-10 weeks	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, inconsistency, imprecision		The mean pain reduction score in the control groups was 5.7	The mean pain reduction score in the intervention groups was 0.8 lower (1.27 to 0.32 lower)
Physical function at ≤3 months (6 minute walk test, feet walked, change scores)	202 (1 study) 4 weeks	⊕⊕⊕⊕ HIGH		The mean change physical function in the control groups was -20	The mean change in physical function in the intervention groups was 19 higher (58 lower to 96 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with TENS versus sham TENS (95% CI)
Psychological distress at ≤3 months (PROMIS depression T scores, high is poor outcome, change scores)	202 (1 study) 4 weeks	⨁⨁⨀⨀ LOW1,2 due to risk of bias, imprecision		The mean change in psychological distress in the control groups was -0.1	The mean change in psychological distress in the intervention groups was 2.7 lower (4.7 to 0.7 lower)
Psychological distress at ≤3 months (PROMIS anxiety T scores, high is poor outcome, change scores)	202 (1 study) 4 weeks	⨁⨁⨁⨀ MODERATE1 due to risk of bias		The mean change in psychological distress in the control groups was -0.6	The mean change in psychological distress in the intervention groups was 0.5 lower (2.7 lower to 1.7 higher)
Pain interference at ≤3 months (BPI interference 0-10, high is poor outcome, change scores)	202 (1 study) 4 weeks	⨁⨁⨀⨀ LOW1,2 due to risk of bias, imprecision		The mean change in pain interference in the control groups was -0.3	The mean change in pain interference in the intervention groups was 0.7 lower (1.3 to 0.1 lower)
Pain self-efficacy at ≤3 months (PSEQ 0-60, high is good outcome, change scores)	202 (1 study) 4 weeks	⨁⨁⨁⨁ HIGH		The mean change in pain self-efficacy in the control groups was 1.5	The mean change in pain self-efficacy in the intervention groups was 1.6 higher (1.8 lower to 5 higher)
Discontinuation at ≤3 months	40 (1 study) 10 weeks	⨁⨁⨀⨀ LOW1,2 due to risk of bias, imprecision	RD 0 (-0.09 to 0.09)	0 per 1000	0 fewer per 1000 (from 90 fewer to 90 more)

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 1 MID or by 2 increments if the confidence interval crossed both MIDs
3 Downgraded for heterogeneity, unexplained by subgroup analysis

Table 7: Clinical evidence summary: TENS versus usual care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with TENS versus sham TENS (95% CI)
Quality of life at ≤3 months (SF36 physical component T scores, high is good outcome, change scores)	202 (1 study) 4 weeks	⊕⊕⊕⊖ MODERATE1 due to risk of bias		The mean change in quality of life score in the control groups was 1.4	The mean change in quality of life score in the intervention groups was 1 higher (0.8 lower to 2.8 higher)
Quality of life at ≤3 months (SF36 mental component T scores, high is good outcome, change scores)	202 (1 study) 4 weeks	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean change in quality of life score in the control groups was 0.04	The mean change in quality of life score in the intervention groups was 2.5 higher (0.6 lower to 5.4 higher)
Pain reduction at ≤3 months (BPI intensity, 0-10, high is poor outcome, change scores)	242 (2 studies) 4-10 weeks	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean change in pain score in the control groups was 0.15	The mean pain reduction score in the intervention groups was 0.9 lower (1.4 to 0.4 lower)
Physical function at ≤3 months (6 minute walk test, feet walked, change scores)	202 (1 study) 4 weeks	⊕⊕⊕⊕ HIGH		The mean change physical function in the control groups was -42.1	The mean change in physical function in the intervention groups was 42 higher (34 lower to 118 higher)
Psychological distress at ≤3 months (PROMIS depression T scores, high is poor outcome, change scores)	202 (1 study) 4 weeks	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean change in psychological distress in the control groups was 0.4	The mean change in psychological distress in the intervention groups was 3.2 lower (5.1 to 1.3 lower)
Psychological distress at ≤3 months (PROMIS anxiety T scores, high is poor outcome, change scores)	202 (1 study) 4 weeks	⊕⊕⊕⊖ MODERATE1 due to risk of bias		The mean change in psychological distress in the control groups was -0.7	The mean change in psychological distress in the intervention groups was 0.4 lower

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with TENS versus sham TENS (95% CI)
					(2.5 lower to 1.7 higher)
Pain interference at ≤3 months (BPI interference 0-10, high is poor outcome, change scores)	202 (1 study) 4 weeks	⨁⨁⊖⊖ LOW1,2 due to risk of bias, imprecision		The mean change in pain interference in the control groups was -0.3	The mean change in pain interference in the intervention groups was 0.6 lower (1.3 lower to 0.1 higher)
Pain self-efficacy at ≤3 months (PSEQ 0-60, high is good outcome, change scores)	202 (1 study) 4 weeks	⨁⨁⨁⨁ HIGH		The mean change in pain self-efficacy in the control groups was 0.8	The mean change in pain self-efficacy in the intervention groups was 2.3 higher (1 lower to 5.6 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 1 MID or by 2 increments if the confidence interval crossed both MIDs.

1 **Table 8: Clinical evidence summary: PENS versus sham PENS**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with PENS versus sham PENS (95% CI)
Quality of life at ≤3 months (NIH-CPSI, 0-12, high is poor outcome, final values)	89 (1 study) 3 months	⨁⨁⊖⊖ LOW1 due to risk of bias		The mean quality of life score in the control groups was 6.7	The mean quality of life score in the intervention groups was 4.6 lower (5.27 to 3.93 lower)
Pain reduction at ≤3 months (VAS, 0-10, high is poor outcome, final values)	89 (1 study) 3 months	⨁⨁⊖⊖ LOW1 due to risk of bias		The mean pain reduction score in the control groups was 7.2	The mean pain reduction score in the intervention groups was 2.9 lower (3.11 to 2.69 lower)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with PENS versus sham PENS (95% CI)
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					

Table 9: Clinical evidence summary: PENS versus usual care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with PENS versus usual care (95% CI)
Quality of life at ≤3 months (SF-36 physical function, 0-100, high is good outcome, final values)	24 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean quality of life score in the control groups was 52.91	The mean quality of life score in the intervention groups was 21.25 higher (0.64 lower to 43.14 higher)
Quality of life at ≤3 months (SF-36 physical role, 0-100, high is good outcome, final values)	24 (1 study) 3 months	⨁⨁⊖⊖ LOW1 due to risk of bias		The mean quality of life score in the control groups was 14.58	The mean quality of life score in the intervention groups was 52.08 higher (23.29 to 80.87 higher)
Quality of life at ≤3 months (SF-36 fatigue, 0-100, high is good outcome, final values)	24 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean quality of life score in the control groups was 45	The mean quality of life score in the intervention groups was 17.91 higher (0.58 to 35.24 higher)
Quality of life at ≤3 months (SF-36 emotional role, 0-100, high is good outcome, final values)	24 (1 study) 3 months	⨁⨁⊖⊖ LOW1 due to risk of bias		The mean quality of life score in the control groups was 13.87	The mean quality of life score in the intervention groups was 47.24 higher (17.93 to 76.55 higher)
Quality of life at ≤3 months (SF-36 mental health, 0-100, high is good outcome, final values)	24 (1 study) 3 months	⨁⨁⊖⊖ LOW1		The mean quality of life score in the control groups	The mean quality of life score 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 Control	Risk difference with PENS versus usual care (95% CI)
		due to risk of bias		was 40.33	20.33 higher (6.31 to 34.35 higher)
Quality of life at ≤3 months (SF-36 social functioning, 0-100, high is good outcome, final values)	24 (1 study) 3 months	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision		The mean quality of life score in the control groups was 50	The mean quality of life score in the intervention groups was 21.87 higher (1.84 to 41.9 higher)
Quality of life at ≤3 months (SF-36 bodily pain, 0-100, high is good outcome, final values)	24 (1 study) 3 months	⊕⊕⊖⊖ LOW1 due to risk of bias		The mean quality of life score in the control groups was 23.33	The mean quality of life score in the intervention groups was 36.67 higher (20.25 to 53.09 higher)
Pain reduction at ≤3 months (VAS, 0-10, high is poor outcome, final values)	24 (1 study) 3 months	⊕⊕⊖⊖ LOW1 due to risk of bias		The mean pain reduction score in the control groups was 7.87	The mean pain reduction score in the intervention groups was 5.25 lower (6.86 to 3.64 lower)

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 1 MID or by 2 increments if the confidence interval crossed both MIDs.

1 **Table 10: Clinical evidence summary: Therapeutic ultrasound versus usual care**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Therapeutic ultrasound versus usual care (95% CI)
Pain reduction at ≤3 months (VAS, 0-10, high is poor outcome, final values)	76 (1 study) 3 months	⊕⊕⊖⊖ LOW1 due to risk of bias		The mean pain score in the control groups was 5.78	The mean pain reduction score in the intervention groups was 2.7 lower (3.54 to 1.86 lower)

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

1 See appendix F for full GRADE tables.

2

1.5 Economic evidence

1.5.1 Included studies

No relevant health economic studies were included.

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

Unit costs of the devices that could be sourced are illustrated below in Table 12.

For some of the interventions it is possible that the equipment can be provided to the patient (or purchased by the patient) and the patient can undertake the intervention themselves (such as TENS). Other types of intervention require that a healthcare professional provides the treatment.

Table 11 demonstrates the costs of staff per hour.

It is common that some interventions such as interferential therapy, laser therapy and ultrasound therapy, are a shared resource that would be available in most physiotherapy departments, and are counted as part of a physiotherapist's appointment.

Table 11: staff costs

Healthcare professional	Cost (per hour)
Community physiotherapist (band 5/6/7)	£52 / £64 / £78

Source: PSSRU 2018[91]

Note: These costs include the ratio of direct to indirect time with patients of 1.37 from the PSSRU. And qualification costs.

Table 12: Electrical physical modalities costs

Intervention	Cost	Source
TENS	£18 - £50	NHS supply chain 2018[261]
Interferential therapy unit (a)	£1128.	NHS supply chain 2014 (based on costs used in the low back pain guideline (NG59))[259]
Laser therapy unit (a)	£955 and £1609	
Ultrasound therapy unit (a)	£853 and £2159	

(a) These interventions were no longer available from the latest version of the NHS supply chain (at the time of writing), however some costs sources are demonstrated in the table taken from the NICE guideline on low back pain. Note these have not been inflated from 2014 as it is not clear if prices of the machines would have increased or decreased since 2014:

1.6 Evidence statements

1.6.2 Clinical evidence statements

1.6.1.3 Laser therapy versus sham laser therapy

4 Quality of life

5 Very low quality evidence from 6 studies with 276 participants showed a clinically important
6 benefit of laser therapy compared to sham laser therapy at ≤3 months. Low to moderate
7 quality evidence from 2 studies with 110 participants showed both a clinically important
8 benefit of laser therapy (physical subscale) and no clinically important difference (mental
9 subscale) compared to sham laser therapy at ≤3 months. Low quality evidence from 2
10 studies with 117 participants showed no clinically important difference compared to sham
11 laser therapy at >3 months.

12 Pain reduction

13 Very low quality evidence from 13 studies with 558 participants showed a clinically important
14 benefit of laser therapy compared to sham laser therapy at ≤3 months. Moderate quality
15 evidence from 2 studies with 71 participants showed a clinically important benefit of laser
16 therapy compared to sham laser therapy at >3 months.

17 Physical function

18 No evidence identified.

19 Psychological distress

20 Low to moderate quality evidence from 1 study with 44 participants showed no clinically
21 important difference between laser therapy and sham laser therapy at ≤3 months.

22 Pain interference

23 No evidence identified.

24 Pain self-efficacy

25 No evidence identified.

26 Use of healthcare services

27 No evidence identified.

28 Sleep

29 No evidence identified.

30 Discontinuation

31 Low quality evidence from 1 study with 90 participants showed no clinically important
32 difference between laser therapy and sham laser therapy at ≤3 months.

1.6.1.2 TMS versus sham TMS

Quality of life

Very low quality evidence from 1 study with 29 participants showed no clinically important difference between TMS and sham TMS at ≤3 months. Low quality evidence from 1 study with 29 participants showed a clinically important benefit of TMS compared to sham TMS at ≤3 months. High quality evidence from 1 study with 51 participants showed a clinically important benefit of TMS compared to sham TMS at ≤3 months. Moderate quality evidence from 1 study with 51 participants showed no clinically important difference between TMS and sham TMS at ≤3 months. Very low quality evidence from 3 studies with 60 participants showed no clinically important difference between TMS and sham TMS at ≤3 months. Very low quality evidence from 1 study with 30 participants showed no clinically important difference between TMS and sham TMS at >3 months.

Pain reduction

Very low quality evidence from 7 studies with 181 participants showed a clinically important benefit of TMS compared to sham TMS at ≤3 months.

Physical function

Very low to moderate quality evidence from 1 study with 20 participants showed no clinically important difference between TMS and sham TMS at ≤3 months.

Psychological distress

Very low quality evidence from 2 studies with 44 participants showed no clinically important difference between TMS and sham TMS at ≤3 months. Moderate quality evidence from 3 studies with 96 participants showed no clinically important difference between TMS and sham TMS at ≤3 months. Very low quality evidence from 1 study with 29 participants showed no clinically important difference between TMS and sham TMS at ≤3 months. Very low quality evidence from 1 study with 30 participants showed no clinically important difference between TMS and sham TMS at >3 months.

Pain interference

Very low quality evidence from 1 study with 30 participants showed a clinically important benefit of TMS compared to sham TMS at >3 months.

Pain self-efficacy

No evidence identified.

Use of healthcare services

No evidence identified.

Sleep

No evidence identified.

Discontinuation

Low quality evidence from 4 studies with 141 participants showed no clinically important difference between TMS and sham TMS at ≤3 months.

1.6.1.3 TDCS versus sham TDCS

Quality of life

Very quality evidence from 1 study with 48 participants showed no clinically important difference between TDCS and sham TDCS at ≤3 months. Moderate to low quality evidence from 1 study with 20 participants showed a clinically important benefit, clinically important harm and no clinically important difference (various subscales) of TDCS compared to sham TDCS at ≤3 months.

Pain reduction

Very low quality evidence from 3 studies with 104 participants showed a clinically important benefit of TDCS compared to sham TDCS at ≤3 months.

Physical function

No evidence identified.

Psychological distress

Very low quality evidence from 2 studies with 84 participants showed a clinically important benefit of TDCS compared to sham TDCS at ≤3 months. Very low quality evidence from 4 studies with 136 participants showed no clinically important difference between TDCS and sham TDCS at ≤3 months.

Pain interference

No evidence identified.

Pain self-efficacy

No evidence identified.

Use of healthcare services

No evidence identified.

Sleep

Moderate quality evidence from 1 study with 20 participants showed a clinically important benefit of TDCS compared to sham TDCS at ≤3 months.

Discontinuation

No evidence identified.

1.6.1.14 TENS versus sham TENS

Quality of life

Moderate quality evidence from 1 study with 202 participants showed no clinically important difference between TENS and sham TENS at ≤3 months.

Pain reduction

Very low quality evidence from 2 studies with 242 participants showed no clinically important difference between TENS and sham TENS at ≤3 months.

Physical function

High quality evidence from 1 study with 202 participants showed no clinically important difference between TENS and sham TENS at ≤3 months.

Psychological distress

Moderate to low quality evidence from 1 study with 202 participants showed no clinically important difference between TENS and sham TENS at ≤3 months.

Pain interference

Low quality evidence from 1 study with 202 participants showed no clinically important difference between TENS and sham TENS at ≤3 months.

Pain self-efficacy

High quality evidence from 1 study with 202 participants showed no clinically important difference between TENS and sham TENS at ≤3 months.

Discontinuation

Low quality evidence from 1 study with 40 participants showed no clinically important difference between TENS and sham TENS at ≤3 months.

No other evidence identified for TENS versus sham TENS.

1.6.1.15 TENS versus usual care

Quality of life

Moderate to low quality evidence from 1 study with 202 participants showed no clinically important difference between TENS and usual care at ≤3 months.

Pain reduction

Low quality evidence from 1 study with 202 participants showed no clinically important difference between TENS and usual care at ≤3 months.

Physical function

High quality evidence from 1 study with 202 participants showed no clinically important difference between TENS and usual care at ≤3 months.

Psychological distress

Moderate to low quality evidence from 1 study with 202 participants showed no clinically important difference between TENS and usual care at ≤3 months.

Pain interference

Low quality evidence from 1 study with 202 participants showed no clinically important difference between TENS and usual care at ≤3 months.

Pain self-efficacy

High quality evidence from 1 study with 202 participants showed no clinically important difference between TENS and usual care at ≤3 months.

No other evidence identified for TENS versus usual care.

1.6.16 PENS versus sham PENS

Quality of life

Low quality evidence from 1 study with 89 participants showed a clinically important benefit of PENS compared to sham PENS at ≤3 months.

Pain reduction

Low quality evidence from 1 study with 89 participants showed a clinically important benefit of PENS compared to sham PENS at ≤3 months.

No other evidence identified for PENS versus sham PENS.

1.6.17 PENS versus usual care

Quality of life

Very low to low quality evidence from 1 study with 24 participants showed a clinically important benefit of PENS compared to usual care at ≤3 months.

Pain reduction

Low quality evidence from 1 study with 24 participants showed a clinically important benefit of PENS compared to usual care at ≤3 months.

No other evidence identified for PENS versus usual care.

1.6.18 Therapeutic ultrasound versus usual care

Pain reduction

Low quality evidence from 1 study with 76 participants showed a clinically important benefit of therapeutic ultrasound compared to usual care at ≤3 months.

No other evidence identified for therapeutic ultrasound versus usual care.

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

The committee considered health-related quality of life, pain reduction, physical function, psychological distress, pain interference and pain self-efficacy to be critical outcomes for decision-making. Use of healthcare services, sleep and discontinuation were also considered to be important outcomes. The critical and important outcomes agreed by the committee were adapted by consensus from relevant core outcome sets registered under the Core Outcome Measures in Effectiveness Trials (COMET) Initiative. This included the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations.

Evidence was identified for all critical outcomes, other than pain interference and pain self-efficacy. Evidence for important outcomes was limited; no evidence was identified for sleep or use of healthcare services, and evidence for discontinuation was limited.

1.7.1.2 The quality of the evidence

Evidence from 34 randomised controlled trials was identified for 8 different comparisons. The comparison with the most evidence was laser therapy versus sham laser therapy. No head-to-head comparisons of different electrical therapies were identified and no evidence was identified for interferential therapy. There was little evidence comparing interventions to usual care.

The majority of the evidence was of low to very low quality. The main reasons for downgrading were risk of bias, inconsistency and imprecision. A large number of studies had small sample sizes, which increased the uncertainty around the point estimates. The evidence for many outcomes included studies that looked at heterogeneous populations, and used different electrical parameters (such as wavelength and voltage) and intervention durations. Where there was heterogeneity in the evidence for an outcome, pre-specified subgroup analyses did not explain the variation in effect sizes. As a result, many outcomes were downgraded for inconsistency.

The committee took into account the low to very low quality of evidence in their discussions, particularly when considering the small amount of evidence for comparisons of TENS, PENS and ultrasound versus sham or usual care.

1.7.1.3 Benefits and harms

Evidence for laser therapy versus sham was based on 14 studies and showed a benefit of treatment in terms of pain and quality of life at short term follow up, although there was serious uncertainty around the effect estimates. The long-term data showing a benefit of laser therapy for pain was based on much smaller sample sizes. Contrastingly, evidence from 2 studies showed no clinically important difference (with some uncertainty) between laser therapy and sham for quality of life at less than 3 months, as measured by the mental component of the SF-36 questionnaire, but there was evidence to suggest a benefit on the physical component of the SF-36. At longer-term follow up, evidence from 2 studies also showed no clinically important difference. The committee noted that they would expect to see a consistent benefit across more domains, if an intervention were to be interpreted as being generally effective. This therefore raised questions about the effectiveness of the intervention for all critical outcomes being assessed. Evidence for psychological distress and discontinuation was limited at less than 3 months, with some low to moderate quality evidence suggesting there was no clinically important benefit of laser therapy, again based

on small sample sizes and with serious uncertainty. No evidence was identified for physical function, pain interference or sleep either in the short or long term. The only long-term evidence was for outcomes of pain and quality of life.

The committee agreed that although there was some evidence of benefit for quality of life and pain, they could not make a recommendation for laser therapy. The evidence from clinical trials was heterogeneous. The physical parameters of the laser light used, the duration of treatment and the time the laser was applied to each painful point varied widely. It was also unclear whether these parameters affected the size, quality and duration of clinical benefit seen within the evidence. This made it difficult for the committee to be confident about the benefits of laser therapy in routine practice, or to make specific recommendations. No cost-effectiveness evidence or evidence assessing longer-term benefit was available. Comparisons were against sham laser therapy, rather than usual care, which is the comparison of greatest interest for implementation in the NHS. Taking all of this into account, the committee agreed they could not make a recommendation for the use of laser therapy in clinical practice. However, they agreed that this preliminary evidence looked promising, and as a result made a recommendation for further research.

Evidence for transcranial magnetic stimulation (TMS) showed a benefit for pain at less than 3 months. This was based on 7 studies, although it was very low quality evidence with serious uncertainty. Evidence for other outcomes, including quality of life, physical function and psychological distress showed no clinical benefit of TMS. Furthermore, the long-term benefit of TMS was unclear with limited evidence. As a result, the committee agreed it could not base a recommendation on pain reduction alone, particularly taking into account the relatively small sample size and low quality of the evidence. The committee instead agreed that the short-term benefit for pain was promising, and that further long-term evidence is needed to determine the effectiveness of TMS. As a result the committee made a recommendation for future research.

Evidence for TENS showed no clinically important difference compared with sham TENS, nor with usual care for quality of life, pain, physical function, psychological distress, pain interference, pain self-efficacy or discontinuation at less than 3 months. The majority of the evidence came from 1 study and the quality of the evidence ranged from high to very low. No longer term evidence was identified. No evidence was identified for ultrasound or interferential therapy. The committee also noted that these technologies have existed for some time and are being used by some in the NHS without evidence of benefit. The committee agreed that resources should be re-allocated to areas with more evidence of clinical and cost effectiveness. Therefore, the committee decided to make a recommendation against the use of TENS, ultrasound and interferential therapy.

The committee also considered the limited evidence identified for TDCS and PENS. Evidence was limited to a small number of studies with small sample sizes. Both interventions showed a benefit for pain, although TDCS showed mixed results for quality of life and psychological distress. PENS on the other hand also showed a benefit for quality of life. However, the evidence was low to very low quality, with uncertainty around the effect sizes. The committee agreed that this evidence was insufficient to determine the effectiveness of each intervention. However, the committee decided not to recommend against these interventions because neither intervention is commonly used in current practice. The committee also decided not to make a research recommendation due to this, and agreed that other areas reviewed across the guideline showed more promising results for future research to be warranted.

1.7.2 Cost effectiveness and resource use

No economic evidence was identified for this question.

It is common that some interventions such as interferential therapy, laser therapy and ultrasound therapy are a shared resource that would be available in most physiotherapy departments, as they might be used for a variety of conditions, and are counted as part of a physiotherapist's appointment. Costs of physiotherapist time were presented to the committee. Some interventions such as TMS are specialist and are not used clinically in the NHS for chronic pain.

There is also a distinction between interventions that the person could self-administer, and do not necessarily require appointments with NHS clinical staff to undertake the intervention. Examples of this would include TENS and TDCS.

If the use of these interventions in general is not widespread across the NHS for people with chronic primary pain, then a positive recommendation in favour of any interventions will require capital outlay to purchase more units to allow the interventions to be more widely available. TENS is relatively cheap and the cheapest of all the interventions to purchase. Costs of the devices for interferential therapy, laser therapy, and ultrasound therapy are not currently available on the NHS supply chain, but the costs of such units that were quoted in the low back pain guideline were presented to the committee as an illustration, which were sourced from the NHS supply chain in 2014.

The committee view of the clinical evidence was that there was considerable uncertainty in the data, with little long-term evidence. Additionally, data on who delivered the intervention was lacking and treatments were relatively short term with a wide range in the number of treatment sessions provided. The intervention which had the largest signal of benefit was laser therapy. This is not widely used in the NHS, and, because of a lack of cost effectiveness evidence of laser therapy, the committee decided to make a research recommendation for laser therapy.

The committee also made some recommendations to not offer some types of electrical physical modalities. This was because there was no or very little evidence, and the committee opinion was that as these are technologies that have been around for some time, no new research was likely to be undertaken. Additionally, they were also aware that as those treatments are being used by some people in the NHS, resources should be re-allocated to areas with more evidence of clinical and cost effectiveness.

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Appendices

Appendix A: Review protocols

Review protocol for electrical physical modalities

ID	Field	Content
0.	PROSPERO registration number	Not registered.
1.	Review title	What is the clinical and cost effectiveness of electrical physical modalities for the management of chronic primary pain?
2.	Review question	What is the clinical and cost effectiveness of electrical physical modalities for the management of chronic primary pain?
3.	Objective	To determine the clinical and cost effectiveness of electrical physical modalities for the management of chronic primary pain.
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	Chronic pain in one or more anatomical regions that is characterized by significant emotional distress (anxiety, anger/frustration or depressed mood) and functional disability (interference in daily life activities and reduced participation in social roles). The diagnosis is appropriate independently of identified biological or psychological contributors unless another diagnosis would better account for the presenting symptoms.
6.	Population	Inclusion: People, aged 16 years and over, with chronic primary pain (whose pain management is not addressed by existing NICE guidance) (chronic widespread pain, complex regional pain syndrome, chronic visceral pain, chronic orofacial pain, chronic primary musculoskeletal pain other than orofacial) Exclusion: Those whose pain management is addressed by existing NICE guidance.
7.	Intervention/Exposure/Test	Interventions: • transcutaneous electrical nerve stimulation (TENS) • percutaneous electrical nerve stimulation (PENS) • interferential therapy • laser therapy • therapeutic ultrasound • transcranial magnetic stimulation (TMS) • transcranial direct current stimulation (TDCS)
8.	Comparator/Reference standard/Confounding factors	Comparators: • each other • placebo/sham • usual care • physical therapies in this guideline.
9.	Types of study to be included	Randomised controlled trials (RCTs) and systematic reviews of RCTs

		Cross-over RCTs will be considered if no non-cross-over RCT evidence is identified.
10.	Other exclusion criteria	Non-English language studies. Studies comparing combinations of interventions.
11.	Context	A clear understanding of the evidence for the effectiveness of chronic primary pain treatments: • improves the confidence of healthcare professionals in their conversations about pain, and • helps healthcare professionals and patients to have realistic expectations about outcomes of treatment.
12.	Primary outcomes (critical outcomes)	• Pain reduction (any validated scale) • health related quality of life (including meaningful activity) • physical function (5 minute walk, sit to stand, Roland Morris Disability Questionnaire, Oswestry Disability Index, Canadian Occupational Performance Measure) • psychological distress (depression/anxiety) (preferably Hospital Anxiety and Depression Scale) • pain interference (brief pain inventory interference subscale) • pain self-efficacy (pain self-efficacy questionnaire). Outcomes will be extracted at the longest time point up to 3 months and at the longest time point after 3 months.
13.	Secondary outcomes (important outcomes)	• Use of healthcare services • sleep • discontinuation. Outcomes will be extracted at the longest time point up to 3 months and at the longest time point after 3 months.
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two

		reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. EviBASE will be used for data extraction. Study investigators may be contacted for missing data where time and resources allow.	
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the Cochrane Risk of Bias (2.0) tool. 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	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). GRADEpro will be used to assess the quality of evidence for 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.	
17.	Analysis of sub-groups	Proposed sensitivity / subgroup analysis to be explored where there is heterogeneity: • chronic widespread pain • complex regional pain syndrome • chronic visceral pain • chronic orofacial pain • chronic primary musculoskeletal pain • cognitive impairment • learning difficulties • first language not English • sensory impairment • homeless	
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	NA – not registered on PROSPERO	
22.	Anticipated completion date	19/08/2020	
23.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail Chronicpain@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre	
24.	Review team members	From the National Guideline Centre: Serena Carville, Guideline Lead Maria Smyth, Senior Systematic Reviewer Rebecca Boffa, Senior Systematic Reviewer	

		Margaret Constanti, Senior Health Economist Joseph Runicles, Information Specialist Katie Broomfield, Project Manager
25.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
26.	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.
27.	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: https://www.nice.org.uk/guidance/indevelopment/gid-ng10069
28.	Other registration details	NA
29.	Reference/URL for published protocol	NA
30.	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.

31.	Keywords	-
32.	Details of existing review of same topic by same authors	NA
33.	Additional information	-
34.	Details of final publication	www.nice.org.uk

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1 **Table 13: Health economic review protocol**

Review question	All questions – health economic evidence
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 2002. 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).[258] **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 2002 or later but that depend on unit costs and resource data entirely or predominantly from before 2002 will be rated as 'Not applicable'. • Studies published before 2002 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.

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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.[258]

For more information, please see the Methods Report published as part of the accompanying documents for this guideline.

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.

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 20 May 2020	Exclusions Randomised controlled trials Systematic review studies
Embase (OVID)	1974 – 20 May 2020	Exclusions Randomised controlled trials Systematic review studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2020 Issue 5 of 12 CENTRAL to 2020 Issue 5 of 12	None

Medline (Ovid) search terms

1.	Chronic pain/
2.	((chronic or persist* or idiopathic or atypical or a-typical) adj4 pain).ti,ab.
3.	exp Complex Regional Pain Syndromes/
4.	(complex regional pain syndrome* or CRPS or causalgia).ti,ab.
5.	((reflex or sympathetic) adj2 dystroph*).ti,ab.
6.	fibromyalgia/
7.	(fibromyalgia* or fibrositis or myofascial pain syndrome).ti,ab.
8.	vulvodynia/
9.	(vulvodynia or vestibulodynia or dyspareunia or vulvar vestibulitis or vulvitis).ti,ab.
10.	interstitial cystitis/
11.	(interstitial adj2 cystitis).ti,ab.
12.	algodystrophy/
13.	(algodystroph* or sudek or sudeck*).ti,ab.
14.	exp myofascial pain syndromes/
15.	cystitis, interstitial/
16.	(loin pain adj (haematuria or hematuria) adj syndrome*).ti,ab.
17.	(LPHS or prostatodynia or CPPS or atypic* odontalgia or a-typic* odontalgia or burning mouth syndrome* or phantom tooth pain or neuropathic orofacial pain or "myofascial pain" or MPS).ti,ab.

18.	((pelvic or pelvis) adj pain syndrome*).ti,ab.
19.	((non-cardiac or noncardiac) adj3 chest adj3 pain).ti,ab.
20.	(temporomandibular adj3 joint adj3 pain).ti,ab.
21.	((prostate or vulv* or bladder or perineal) adj3 pain).ti,ab.
22.	(functional pain syndrome* or non-cancer pain or noncancer pain).ti,ab.
23.	((pelvic or pelvis or abdominal) adj3 pain adj3 (unknown or un-known or idiopathic or atypic* or a-typic*)).ti,ab.
24.	or/1-23
25.	letter/
26.	editorial/
27.	news/
28.	exp historical article/
29.	Anecdotes as Topic/
30.	comment/
31.	case report/
32.	(letter or comment*).ti.
33.	or/25-32
34.	randomized controlled trial/ or random*.ti,ab.
35.	33 not 34
36.	animals/ not humans/
37.	exp Animals, Laboratory/
38.	exp Animal Experimentation/
39.	exp Models, Animal/
40.	exp Rodentia/
41.	(rat or rats or mouse or mice).ti.
42.	or/35-41
43.	24 not 42
44.	limit 43 to English language
45.	Transcutaneous Electric Nerve Stimulation/
46.	(TENS or PENS or ALTENS or TNS or TENMS or TMS or TDCS).ti,ab.
47.	(electroanalges* or electro analges*).ti,ab.
48.	Electric Stimulation Therapy/
49.	electrotherap*.ti,ab.
50.	((transcutaneous or transcranial or percutaneous or cutaneous or transderm* or peripheral or microamperage) adj3 (stimulat* or electr*)).ti,ab.
51.	electrostimulat*.ti,ab.
52.	(interferential adj2 current*).ti,ab.
53.	((electric* or electro or interferential) adj2 (stimulat* or therap* or acupuncture)).ti,ab.
54.	Laser Therapy, Low-Level/
55.	(laser adj2 (therap* or treat* or phototherap* or irradiat* or biostimulat* or stimulat*)).ti,ab.
56.	Ultrasonic Therapy/ or Extracorporeal Shockwave Therapy/
57.	((ultrasound or ultra sound or ultrasonic or ultra sonic) adj3 (contin* or therap* or treat* or stimulat* or intervention*)).ti,ab.
58.	or/45-57
59.	randomized controlled trial.pt.
60.	controlled clinical trial.pt.
61.	randomi#ed.ti,ab.

62.	placebo.ab.
63.	randomly.ti,ab.
64.	Clinical Trials as topic.sh.
65.	trial.ti.
66.	or/59-65
67.	Meta-Analysis/
68.	exp Meta-Analysis as Topic/
69.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
70.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
71.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
72.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
73.	(search* adj4 literature).ab.
74.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
75.	cochrane.jw.
76.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
77.	or/67-76
78.	44 and 58 and (66 or 77)

1 **Embase (Ovid) search terms**

1.	Chronic pain/
2.	((chronic or persist* or idiopathic or atypical or a-typical) adj4 pain).ti,ab.
3.	exp Complex regional pain syndrome/
4.	(complex regional pain syndrome* or CRPS or causalgia).ti,ab.
5.	((reflex or sympathetic) adj2 dystroph*).ti,ab.
6.	fibromyalgia/
7.	(fibromyalgia* or fibrositis or myofascial pain syndrome).ti,ab.
8.	vulvodynia/
9.	(vulvodynia or vestibulodynia or dyspareunia or vulvar vestibulitis or vulvitis).ti,ab.
10.	interstitial cystitis/
11.	(interstitial adj2 cystitis).ti,ab.
12.	algodystrophy/
13.	(algodystroph* or sudek or sudeck*).ti,ab.
14.	myofascial pain/
15.	noncardiac chest pain/
16.	cystalgia/
17.	Pelvis pain syndrome/
18.	(loin pain adj (haematuria or hematuria) adj syndrome*).ti,ab.
19.	(LPHS or prostatodynia or CPPS or atypic* odontalgia or a-typic* odontalgia or burning mouth syndrome* or phantom tooth pain or neuropathic orofacial pain or "myofascial pain" or MPS).ti,ab.
20.	((pelvic or pelvis) adj pain syndrome*).ti,ab.
21.	((non-cardiac or noncardiac) adj3 chest adj3 pain).ti,ab.
22.	(temporomandibular adj3 joint adj3 pain).ti,ab.
23.	((prostate or vulv* or bladder or perineal) adj3 pain).ti,ab.
24.	(functional pain syndrome* or non-cancer pain or noncancer pain).ti,ab.

25.	((pelvic or pelvis or abdominal) adj3 pain adj3 (unknown or un-known or idiopathic or atypic* or a-typic*)).ti,ab.
26.	or/1-25
27.	letter.pt. or letter/
28.	note.pt.
29.	editorial.pt.
30.	case report/ or case study/
31.	(letter or comment*).ti.
32.	or/27-31
33.	randomized controlled trial/ or random*.ti,ab.
34.	32 not 33
35.	animal/ not human/
36.	nonhuman/
37.	exp Animal Experiment/
38.	exp Experimental Animal/
39.	animal model/
40.	exp Rodent/
41.	(rat or rats or mouse or mice).ti.
42.	or/34-41
43.	26 not 42
44.	limit 43 to English language
45.	transcutaneous nerve stimulation/
46.	electrostimulation therapy/
47.	(TENS or PENS or ALTENS or TNS or TENMS or TMS or TDCS).ti,ab.
48.	(electroanalges* or electro analges*).ti,ab.
49.	electrotherap*.ti,ab.
50.	((transcutaneous or transcranial or percutaneous or cutaneous or transderm* or peripheral or microamperage) adj3 (stimulat* or electr*)).ti,ab.
51.	electrostimulat*.ti,ab.
52.	(interferential adj2 current*).ti,ab.
53.	((electric* or electro or interferential) adj2 (stimulat* or therap* or acupuncture)).ti,ab.
54.	(laser adj2 (therap* or treat* or phototherap* or irradiat* or biostimulat* or stimulat*)).ti,ab.
55.	Ultrasonic Therapy/
56.	((ultrasound or ultra sound or ultrasonic or ultra sonic) adj3 (contin* or therap* or treat* or stimulat* or intervention*)).ti,ab.
57.	low level laser therapy/
58.	electroanalgesia/
59.	or/45-58
60.	44 and 59
61.	random*.ti,ab.
62.	factorial*.ti,ab.
63.	(crossover* or cross over*).ti,ab.
64.	((doubl* or singl*) adj blind*).ti,ab.
65.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
66.	crossover procedure/
67.	single blind procedure/
68.	randomized controlled trial/

69.	double blind procedure/
70.	or/61-69
71.	systematic review/
72.	meta-analysis/
73.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
74.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
75.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
76.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
77.	(search* adj4 literature).ab.
78.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
79.	cochrane.jw.
80.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
81.	or/71-80
82.	60 and (70 or 81)

1 **Cochrane Library (Wiley) search terms**

#1.	MeSH descriptor: [Chronic Pain] explode all trees
#2.	((chronic or persist* or idiopathic or atypical or a-typical) near/4 pain):ti,ab
#3.	MeSH descriptor: [Complex Regional Pain Syndromes] explode all trees
#4.	(complex regional pain syndrome* or CRPS or causalgia):ti,ab
#5.	((reflex or sympathetic) near/2 dystroph*):ti,ab
#6.	MeSH descriptor: [Fibromyalgia] explode all trees
#7.	(fibromyalgia* or fibrositis or myofascial pain syndrome):ti,ab
#8.	MeSH descriptor: [Vulvodynia] explode all trees
#9.	(vulvodynia or vestibulodynia or dyspareunia or vulvar vestibulitis or vulvitis):ti,ab
#10.	MeSH descriptor: [Cystitis, Interstitial] explode all trees
#11.	(interstitial near/2 cystitis):ti,ab
#12.	MeSH descriptor: [Reflex Sympathetic Dystrophy] explode all trees
#13.	(algodystroph* or sudek or sudeck*):ti,ab
#14.	MeSH descriptor: [Myofascial Pain Syndromes] explode all trees
#15.	(loin pain near (haematuria or hematuria) near syndrome*):ti,ab
#16.	(LPHS or prostatodynia or CPPS or atypic* odontalgia or a-typic* odontalgia or burning mouth syndrome* or phantom tooth pain or neuropathic orofacial pain or "myofascial pain" or MPS):ti,ab
#17.	((pelvic or pelvis) near pain syndrome*):ti,ab
#18.	((non-cardiac or noncardiac) near/3 chest near/3 pain):ti,ab
#19.	(temporomandibular near/3 joint near/3 pain):ti,ab
#20.	((prostate or vulv* or bladder or perineal) near/3 pain):ti,ab
#21.	(functional pain syndrome* or non-cancer pain or noncancer pain):ti,ab
#22.	((pelvic or pelvis or abdominal) near/3 pain near/3 (unknown or un-known or idiopathic or atypic* or a-typic*)):ti,ab
#23.	(or #1-#22)
#24.	MeSH descriptor: [Transcutaneous Electric Nerve Stimulation] explode all trees
#25.	(TENS or PENS or ALTENS or TNS or TENMS or TMS or TDCS):ti,ab
#26.	(electroanalges* or electro analges*):ti,ab
#27.	MeSH descriptor: [Electric Stimulation Therapy] explode all trees

#28.	electrotherap*:ti,ab
#29.	((transcutaneous or transcranial or percutaneous or cutaneous or transderm* or peripheral or microamperage) near/3 (stimulat* or electr*)):ti,ab
#30.	electrostimulat*:ti,ab
#31.	(interferential near/2 current*):ti,ab
#32.	((electric* or electro or interferential) near/2 (stimulat* or therap* or acupuncture)):ti,ab
#33.	MeSH descriptor: [Laser Therapy] explode all trees
#34.	(laser near/2 (therap* or treat* or phototherap* or irradiat* or biostimulat* or stimulat*)):ti,ab
#35.	MeSH descriptor: [Ultrasonic Therapy] explode all trees
#36.	MeSH descriptor: [Extracorporeal Shockwave Therapy] explode all trees
#37.	((ultrasound or ultra sound or ultrasonic or ultra sonic) near/3 (contin* or therap* or treat* or stimulat* or intervention*)):ti,ab
#38.	(or #24-#37)
#39.	#23 and #38

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to a Chronic Pain 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 economic modelling.

Table 14: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014 – 20 May 2020	Exclusions Health economics studies Health economics modelling studies
Embase	2014 – 20 May 2020	Exclusions Health economics studies Health economics modelling studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 20 May 2020 NHSEED - Inception to March 2015	None

Medline search terms

1.	chronic pain/ or pain, intractable/
2.	((persist* or intract* or chronic or longstanding or long standing or longterm or long term or refractory or prolong* or long last* or sustain* or linger* or syndrome*) adj3 pain*).ti,ab.
3.	((chronic or persist* or idiopathic or atypical or a-typical) adj4 pain).ti,ab.
4.	exp Complex Regional Pain Syndromes/
5.	(complex regional pain syndrome* or CRPS or causalgia).ti,ab.

6.	fibromyalgia/
7.	((reflex or sympathetic) adj2 dystroph*).ti,ab.
8.	vulvodynia/
9.	(vulvodynia or vestibulodynia or dyspareunia or vulvar vestibulitis or vulvitis).ti,ab.
10.	interstitial cystitis/
11.	(interstitial adj2 cystitis).ti,ab.
12.	algodystrophy/
13.	(algodystroph* or sudek or sudeck*).ti,ab.
14.	exp myofascial pain syndromes/
15.	cystitis, interstitial/
16.	(loin pain adj (haematuria or hematuria) adj syndrome*).ti,ab.
17.	(LPHS or prostatodynia or CPPS or atypic* odontalgia or a-typic* odontalgia or burning mouth syndrome* or phantom tooth pain or neuropathic orofacial pain or "myofascial pain" or MPS).ti,ab.
18.	((pelvic or pelvis) adj pain syndrome*).ti,ab.
19.	((non-cardiac or noncardiac) adj3 chest adj3 pain).ti,ab.
20.	(temporomandibular adj3 joint adj3 pain).ti,ab.
21.	((prostate or vulv* or bladder or perineal) adj3 pain).ti,ab.
22.	(functional pain syndrome* or non-cancer pain or noncancer pain).ti,ab.
23.	((pelvic or pelvis or abdominal) adj3 pain adj3 (unknown or un-known or idiopathic or atypic* or a-typic*)).ti,ab.
24.	(fibromyalgia* or fibrositis or myofascial pain syndrome).ti,ab.
25.	or/1-24
26.	letter/
27.	editorial/
28.	news/
29.	exp historical article/
30.	Anecdotes as Topic/
31.	comment/
32.	case report/
33.	(letter or comment*).ti.
34.	or/26-33
35.	randomized controlled trial/ or random*.ti,ab.
36.	34 not 35
37.	animals/ not humans/
38.	exp Animals, Laboratory/
39.	exp Animal Experimentation/
40.	exp Models, Animal/
41.	exp Rodentia/
42.	(rat or rats or mouse or mice).ti.
43.	or/36-42
44.	25 not 43
45.	Economics/
46.	Value of life/
47.	exp "Costs and Cost Analysis"/
48.	exp Economics, Hospital/
49.	exp Economics, Medical/
50.	Economics, Nursing/

51.	Economics, Pharmaceutical/
52.	exp "Fees and Charges"/
53.	exp Budgets/
54.	budget*.ti,ab.
55.	cost*.ti.
56.	(economic* or pharmaco?economic*).ti.
57.	(price* or pricing*).ti,ab.
58.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
59.	(financ* or fee or fees).ti,ab.
60.	(value adj2 (money or monetary)).ti,ab.
61.	or/45-60
62.	exp models, economic/
63.	*Models, Theoretical/
64.	*Models, Organizational/
65.	markov chains/
66.	monte carlo method/
67.	exp Decision Theory/
68.	(markov* or monte carlo).ti,ab.
69.	econom* model*.ti,ab.
70.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
71.	or/62-70
72.	44 and (61 or 71)

1 **Embase (Ovid) search terms**

1.	chronic pain/ or pain, intractable/
2.	((persist* or intract* or chronic or longstanding or long standing or longterm or long term or refractory or prolong* or long last* or sustain* or linger* or syndrome*) adj3 pain*).ti,ab.
3.	((chronic or persist* or idiopathic or atypical or a-typical) adj4 pain).ti,ab.
4.	exp Complex regional pain syndrome/
5.	(complex regional pain syndrome* or CRPS or causalgia).ti,ab.
6.	((reflex or sympatheti) adj2 dystroph*).ti,ab.
7.	fibromyalgia/
8.	(fibromyalgia* or fibrositis or myofascial pain syndrome).ti,ab.
9.	vulvodynia/
10.	(vulvodynia or vestibulodynia or dyspareunia or vulvar vestibulitis or vulvitis).ti,ab.
11.	interstitial cystitis/
12.	(interstitial adj2 cystitis).ti,ab.
13.	algodystrophy/
14.	(algodystroph* or sudek or sudeck*).ti,ab.
15.	myofascial pain/
16.	noncardiac chest pain/
17.	cystalgia/
18.	Pelvis pain syndrome/
19.	(loin pain adj (haematuria or hematuria) adj syndrome*).ti,ab.
20.	(LPHS or prostatodynia or CPPS or atypic* odontalgia or a-typic* odontalgia or burning mouth syndrome* or phantom tooth pain or neuropathic orofacial pain or "myofascial pain" or MPS).ti,ab.

21.	((pelvic or pelvis) adj pain syndrome*).ti,ab.
22.	((non-cardiac or noncardiac) adj3 chest adj3 pain).ti,ab.
23.	(temporomandibular adj3 joint adj3 pain).ti,ab.
24.	((prostate or vulv* or bladder or perineal) adj3 pain).ti,ab.
25.	(functional pain syndrome* or non-cancer pain or noncancer pain).ti,ab.
26.	((pelvic or pelvis or abdominal) adj3 pain adj3 (unknown or un-known or idiopathic or atypic* or a-typic*)).ti,ab.
27.	or/1-26
28.	letter.pt. or letter/
29.	note.pt.
30.	editorial.pt.
31.	case report/ or case study/
32.	(letter or comment*).ti.
33.	or/28-32
34.	randomized controlled trial/ or random*.ti,ab.
35.	33 not 34
36.	animal/ not human/
37.	nonhuman/
38.	exp Animal Experiment/
39.	exp Experimental Animal/
40.	animal model/
41.	exp Rodent/
42.	(rat or rats or mouse or mice).ti.
43.	or/35-42
44.	27 not 43
45.	health economics/
46.	exp economic evaluation/
47.	exp health care cost/
48.	exp fee/
49.	budget/
50.	funding/
51.	budget*.ti,ab.
52.	cost*.ti.
53.	(economic* or pharmaco?economic*).ti.
54.	(price* or pricing*).ti,ab.
55.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
56.	(financ* or fee or fees).ti,ab.
57.	(value adj2 (money or monetary)).ti,ab.
58.	or/45-57
59.	statistical model/
60.	exp economic aspect/
61.	59 and 60
62.	*theoretical model/
63.	*nonbiological model/
64.	stochastic model/
65.	decision theory/
66.	decision tree/

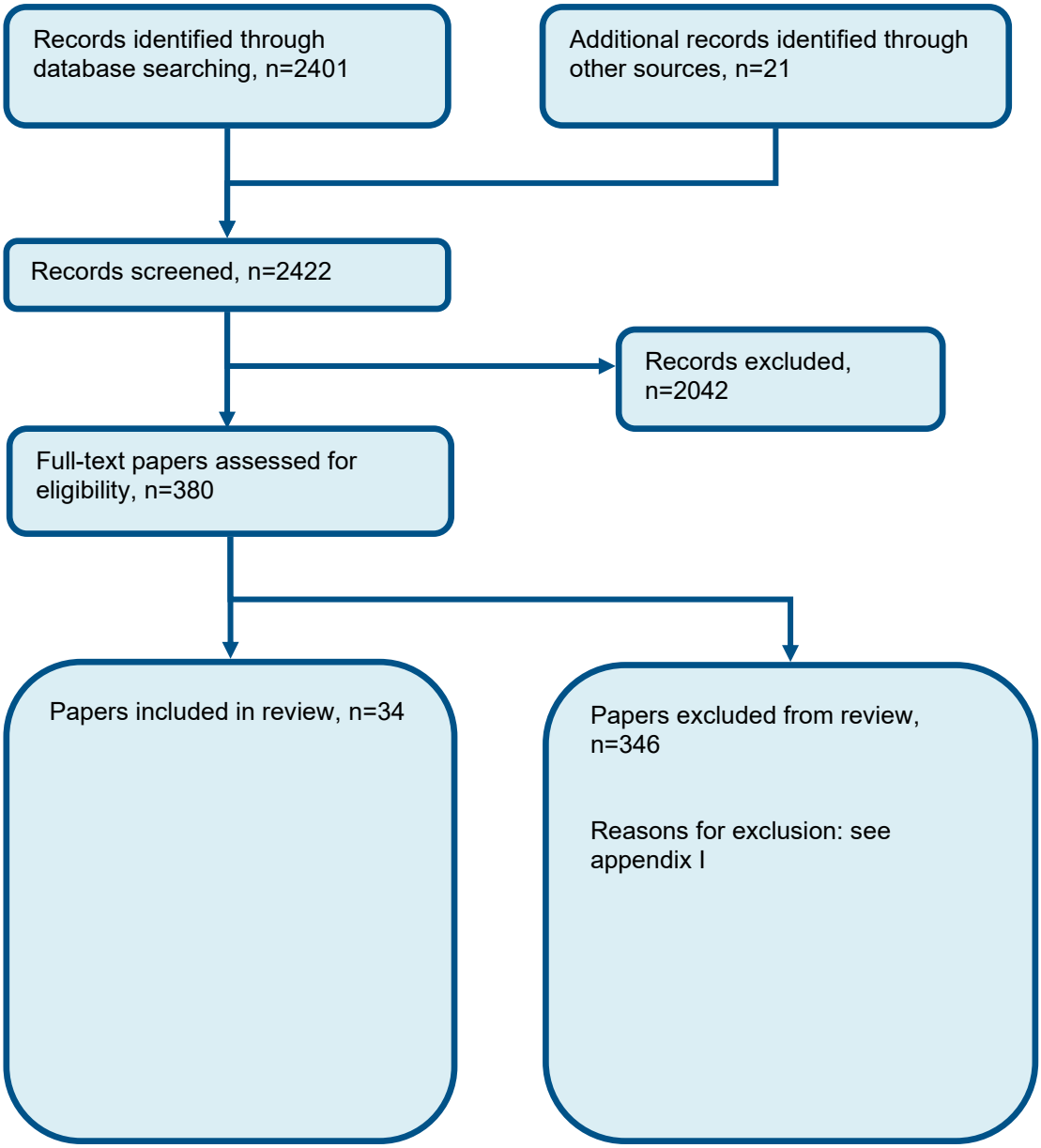
67.	monte carlo method/
68.	(markov* or monte carlo).ti,ab.
69.	econom* model*.ti,ab.
70.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
71.	or/61-70
72.	44 and (58 or 71)

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Chronic Pain EXPLODE ALL TREES
#2.	(((persist* or intract* or chronic or longstanding or long standing or longterm or long term or refractory or prolong* or long last* or sustain* or linger* or syndrome*) adj3 pain*))
#3.	(((chronic or persist* or idiopathic or atypical or a-typical) adj4 pain))
#4.	MeSH DESCRIPTOR Complex Regional Pain Syndromes EXPLODE ALL TREES
#5.	((complex regional pain syndrome* or CRPS or causalgia))
#6.	MeSH DESCRIPTOR Fibromyalgia EXPLODE ALL TREES
#7.	(((reflex or sympathetic) adj2 dystroph*))
#8.	MeSH DESCRIPTOR Vulvodynia EXPLODE ALL TREES
#9.	((vulvodynia or vestibulodynia or dyspareunia or vulvar vestibulitis or vulvitis))
#10.	MeSH DESCRIPTOR Cystitis, Interstitial EXPLODE ALL TREES
#11.	((interstitial adj2 cystitis))
#12.	MeSH DESCRIPTOR Reflex Sympathetic Dystrophy EXPLODE ALL TREES
#13.	((algodystroph* or sudek or sudeck*))
#14.	MeSH DESCRIPTOR Myofascial Pain Syndromes EXPLODE ALL TREES
#15.	((loin pain adj (haematuria or hematuria) adj syndrome*))
#16.	((LPHS or prostatodynia or CPPS or atypic* odontalgia or a-typic* odontalgia or burning mouth syndrome* or phantom tooth pain or neuropathic orofacial pain or "myofascial pain" or MPS))
#17.	(((pelvic or pelvis) adj pain syndrome*))
#18.	(((non-cardiac or noncardiac) adj3 chest adj3 pain))
#19.	((temporomandibular adj3 joint adj3 pain))
#20.	(((prostate or vulv* or bladder or perineal) adj3 pain))
#21.	((functional pain syndrome* or non-cancer pain or noncancer pain))
#22.	(((pelvic or pelvis or abdominal) adj3 pain adj3 (unknown or un-known or idiopathic or atypic* or a-typic*)))
#23.	((fibromyalgia* or fibrositis or myofascial pain syndrome))
#24.	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23)

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of electrical physical modalities



Appendix D: Clinical evidence tables

Study	Altan 2005[19]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=53)
Countries and setting	Conducted in Turkey; Setting: Not stated
Line of therapy	Unclear
Duration of study	Intervention + follow up: 2 weeks + 3 months
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: Only state inclusion criteria, not assessment method
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	1. Localised pain and taut bands in the neck for a minimum of the previous 3 months; 2. Bilateral and significantly more tenderness in the three cervical trigger points (midpoint and the upper border of the trapezius muscle, origin of the supraspinatus muscle, and insertion of the sub occipital muscle) compared to the control point (a non0tender point over deltoid muscle). These three trigger points are among the 18 described for FMS according to 1990 American College of Rheumatology criteria; 3. Existence of no other criterion for FMS diagnosis; 4. No history or finding of cervical arthrosis, discal hernia, cervical vertebral fracture, radiculopathy, or myelopathy; 5. No pathological finding in blood count, urinalysis, sedimentation or cervical X-ray.
Exclusion criteria	Only inclusion criteria stated.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Laser group 43.48 (2.42) ; Placebo group 43.32 (2.1). Gender (M:F): 16/32. Ethnicity: Not stated
Further population details	Chronic primary musculoskeletal pain

Extra comments	Duration of symptoms in years, mean (SD): Laser group 4.74 (1.3) Placebo group 4.38 (1.21).
Indirectness of population	No indirectness
Interventions	(n=26) Intervention 1: Electrical Physical Modalities - Laser therapy. GaAs laser treatment was applied over the three trigger points bilaterally and also one point in the taut bands in trapezius muscle bilaterally with a frequency of 1000 Hz for 2 min over each point once a day for 10 weekdays during a period of 2 weeks. The head of the instrument was held perpendicularly to and in slight contact with the skin. The infrared-27 GaAs diode laser instrument (Roland Serie Elettronica Pagani) with a wavelength of 904 nm, frequency range of 5-7000 Hz, and maximum power of 27 W, 50 W, or 27x4 W was used. Duration 2 weeks (10 sessions). Concurrent medication/care: All patients were instructed not to take nonsteroidal anti-inflammatory drugs (NSAID) or any other analgesic during the treatment and control periods. All patients in both groups were instructed to perform daily isometric exercises and stretching just short of pain 2 weeks at home. Indirectness: No indirectness. (n=27) Intervention 2: Placebo/Sham. A placebo laser treatment was given by using the same instrument in the same way over the same points as in the intervention group but not turning it on. Duration 2 weeks (10 sessions). Concurrent medication/care: All patients were instructed not to take nonsteroidal anti-inflammatory drugs (NSAID) or any other analgesic during the treatment and control periods. All patients in both groups were instructed to perform daily isometric exercises and stretching just short of pain 2 weeks at home. Indirectness: No indirectness
Funding	Funding not stated

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

Protocol outcome 1: Pain reduction
- Actual outcome: Pain intensity (VAS) at 2 weeks (end of treatment); Group 1: mean 4.13 (SD 0.58); n=23, Group 2: mean 3.92 (SD 0.42); n=25; Visual analogue scale (VAS) 0-10 Top=High is poor outcome; Comments: Baselines, mean (SD):
Laser group 6.85 (0.35)
Placebo group 6.24 (0.32)
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 ; Baseline details: VAS baselines, mean (SD):
Laser group 6.85 (0.35)
Placebo group 6.24 (0.32); Group 1 Number missing: 3, Reason: Not available for treatment stage.; Group 2 Number missing: 2, Reason: Not available for

treatment stage. - Actual outcome: Pain intensity (VAS) at 14 weeks; Group 1: mean 3.17 (SD 0.58); n=23, Group 2: mean 3.8 (SD 0.51); n=25; Visual analogue scale (VAS) 0-10 Top=High is poor outcome; Comments: Baselines, mean (SD): Laser group 6.85 (0.35) Placebo group 6.24 (0.32) 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 ; Baseline details: VAS baselines, mean (SD): Laser group 6.85 (0.35) Placebo group 6.24 (0.32); Group 1 Number missing: 3, Reason: Not available for treatment stage.; Group 2 Number missing: 2, Reason: Not available for treatment stage.	
Protocol outcomes not reported by the study	Quality of life ; Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

Study	Arbabi-kalati 2015[28]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=20)
Countries and setting	Conducted in Iran; Setting: Zahedan University of Medical Sciences
Line of therapy	Unclear
Duration of study	Intervention time: 2 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Burning mouth patients referred from Zahedan Faculty of Dentistry
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosis criteria: 1) burning sensation in all or a part of the oral cavity with or without symptoms such as a change in taste sensation for at least 4 months; 2) normal oral mucosa without any lesion; 3) absence of any local or systemic factors which produce the same symptoms.
Exclusion criteria	Any known systemic condition; patients under 18; pregnancy; smoking; patients with oral legions; patients not signing the informed consent form.
Recruitment/selection of patients	Referred from Zahedan Faculty of Dentistry
Age, gender and ethnicity	Age - Mean (SD): Laser group 47.2(+-5.3) ; Placebo group 46.6(+-4.6). Gender (M:F): 0/20. Ethnicity: Not reported
Further population details	1. Chronic orofacial pain
Extra comments	Duration of disease in months, mean+-SD: Laser group 13.4+-7.4(6-30) ; 15.5+-0.1(6-36)
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: Electrical Physical Modalities - Laser therapy. Low Level Laser Therapy (LLLT), wavelength 630 nm, power of 30 mW for 10 seconds, using an Iodine-Gallium-Aresnide laser of Mustange laser device (Russia). Laser dose 1 j/cm2. Applied to 10 areas on the oral mucosa, 2 areas on the tongue, 2 areas on the floor of the mouth, 1 area on the soft palate and 1 area on the soft palate. Duration Twice a week for 2 weeks.

	Concurrent medication/care: None stated. Indirectness: No indirectness. (n=10) Intervention 2: Placebo/Sham. Silent/off laser therapy carried out for the same period and at the same points as the laser treatment group. Participants wore protective glasses, blinding them to the type of treatment modality used. Duration Twice a week for 2 weeks. Concurrent medication/care: None stated. Indirectness: No indirectness
Funding	Academic or government funding (Zahedan University of Medical Sciences)

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

Protocol outcome 1: Quality of life
- Actual outcome: Quality of life questionnaire at After treatment (2 weeks); Group 1: mean 12.8 (SD 11.4); n=10, Group 2: mean 28.6 (SD 11.5); n=10; Quality of life questionnaire (Persian version of Oral Health Impact Profile) 0-40 Top=High is poor outcome; Comments: Baseline, mean (SD):
Laser group 27.8 (12)
Placebo group 28.3 (11.9)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Outcome baselines comparable; Group 1 Number missing; Group 2 Number missing

Protocol outcome 2: Pain reduction
- Actual outcome: Pain on numeric rating scale at After treatment (2 weeks); Group 1: mean 3.6 (SD 3); n=10, Group 2: mean 8 (SD 1.5); n=10; Numeric rating scale (for severity of burning sensation) 0-10 Top=High is poor outcome; Comments: Baselines, mean (SD):
Laser group 8 (2.3)
Placebo group 8.2 (1.7)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Outcome baselines comparable.; Group 1 Number missing; Group 2 Number missing

Protocol outcomes not reported by the study	Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

Study	Armagan 2006[31]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=32)
Countries and setting	Conducted in Turkey; Setting: Physical Therapy and Rehabilitation department of Osmangazi University hospital
Line of therapy	Unclear
Duration of study	Intervention + follow up: 10 day intervention and 6 month follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ACR criteria for fibromyalgia
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Widespread pain for at least 3 months located on both sides of the body and above and below the waist, the presence of at least 11 of 18 tender points on digital palpation
Exclusion criteria	Inflammatory causes of pain, inability to interrupt therapy with medications, presence of other conditions that could influence pain or response to treatment or ability to take part in treatment, pregnancy, major psychiatric disorders.
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Mean (SD): 38.25 (5.36) years. Gender (M:F): All women. Ethnicity: Not specified
Further population details	Chronic widespread pain
Extra comments	Mean duration of pain 5.8 (3.2) years
Indirectness of population	No indirectness
Interventions	(n=16) Intervention 1: Electrical Physical Modalities - Laser therapy. Gal-Al-As diode laser device used with a power output of 50mW and a wavelength of 830nm. Diameter of laser beam 1mm, and laser was set to deliver a continuous form of energy, for 1 minute periods at each tender point (2 joules per tender joint). Once a day, 5 days a week for a total duration of 10 days and all participants treated by the same physician. Duration 10 days. Concurrent medication/care: Not specified. Indirectness: No indirectness

	(n=16) Intervention 2: Placebo/Sham. Placebo laser therapy. The same treatment protocol and the laser device appeared to patients to be working, but no laser beam was transferred to the treated area, and all painful points were irradiated. Duration 10 days. Concurrent medication/care: Not specified. Indirectness: No indirectness.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LASER THERAPY versus PLACEBO/SHAM Protocol outcome 1: Quality of life - Actual outcome: FIQ at 10 days; Group 1: mean 58.5 (SD 10.33); n=16, Group 2: mean 63.63 (SD 9.59); n=16; FIQ 0-100 Top=High is poor outcome; Comments: Baseline: 65.5(9.01);65.38(9.44) 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: FIQ at 6 months; Group 1: mean 62.06 (SD 8.99); n=16, Group 2: mean 66.94 (SD 8.44); n=16; FIQ 0-100 Top=High is poor outcome; Comments: Baseline: 65.5(9.01);65.38(9.44) 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.	
Protocol outcomes not reported by the study	Pain reduction ; Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

Study	Bardellini 2019[37]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=90)
Countries and setting	Conducted in Italy; Setting: Department of oral medicine
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 10 weeks + 1 month
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: complaint of oral pain or burning for more than 6 months
Stratum	Overall: NA
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	Patients who had complained of oral pain or burning for more than 6 months
Exclusion criteria	age under 18 years, pregnancy, oral mucosal lesions, systemic disease (hypertension, diabetes, anaemia, vitamin B12 or folic acid deficiency.), gastro-esophageal reflux, Sjogren's syndrome, allergies, and hyposalivation; positivity to Candidida or other microorganisms
Recruitment/selection of patients	consecutive meeting the inclusion criteria
Age, gender and ethnicity	Age - Mean (SD): laser group: 59.76 (9.51) years, sham group: 60.86 (10.02) years . Gender (M:F): all female. Ethnicity: not reported

Further population details	1. Chronic orofacial pain: Chronic orofacial pain 2. Chronic primary musculoskeletal pain: Pain other than chronic primary musculoskeletal pain 3. Chronic visceral pain: Pain other than chronic visceral pain 4. Chronic widespread pain: Pain other than chronic widespread pain 5. Cognitive impairment: Not stated / Unclear 6. Complex regional pain syndrome: Pain other than complex regional pain syndrome 7. First language not English: Not applicable 8. Homeless: Not stated / Unclear 9. Learning difficulties: Not stated / Unclear 10. Sensory impairment : Not stated / Unclear
Indirectness of population	No indirectness: NA
Interventions	(n=45) Intervention 1: Electrical Physical Modalities - Laser therapy. The laser instrument used for this trial was K Laser Cube 3®. The laser was applied by a trained dentist and irradiated the most painful areas in the oral cavity, with discontinuous combined wavelengths between 660-970 nm, medium power 3.2 W (6.4 W pulsed at 50%), treatment time 3'51", frequency 1-20000Hz, spot size 1cm². Treatment was once a week for 10 weeks. Duration 10 weeks . Concurrent medication/care: Not reported . Indirectness: No indirectness; Indirectness comment: NA Comments: NA (n=45) Intervention 2: Placebo/Sham. The device was turned on but the hand piece did not work. Laser/sham therapy was dispensed once a week for ten weeks. Duration 10 weeks . Concurrent medication/care: Not reported . Indirectness: No indirectness; Indirectness comment: NA Comments: NA
Funding	Funding not stated

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

Protocol outcome 1: Quality of life
- Actual outcome: Oral Health Impact Profile questionnaire (OHIP-14)
at 10 weeks ; Group 1: mean 7.09 (SD 2.59); n=43, Group 2: mean 10.64 (SD 4.13); n=42; OHIP-14 (Italian version) 0-56 Top=High is poor outcome; Comments: Baseline values: laser group 16.09 (4.2), sham group 15.26 (3.75)
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, Comments: NA; Group 1 Number missing: 2, Reason: did not complete therapy; Group 2 Number missing: 3, Reason: did not complete therapy - Actual outcome: Oral Health Impact Profile questionnaire (OHIP-14) at 14 weeks (10 weeks + 1 month follow up); Group 1: mean 7.43 (SD 3.78); n=43, Group 2: mean 10.43 (SD 2.99); n=42; OHIP-14 (Italian version) 0-56 Top=High is poor outcome; Comments: Baseline values: laser group 16.09 (4.2), sham group 15.26 (3.75) 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, Comments: NA; Group 1 Number missing: 2, Reason: did not complete therapy; Group 2 Number missing: 3, Reason: did not complete therapy	
Protocol outcomes not reported by the study	Pain reduction; Physical function; Psychological distress; Pain interference; Pain self-efficacy; Use of healthcare services; Sleep; Discontinuation

Study	Boyer 2014[53]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=38)
Countries and setting	Conducted in France; Setting: La Timone University Hospital pain centre
Line of therapy	Unclear
Duration of study	Intervention time: 10 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ACR FMS criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged >18 years, right handed, diagnosis of FMS according to ACR, score of at least 4 on the BPI average pain intensity scale, pain for more than 6 months, stable treatment for more than 1 month before enrolment, rTMS naive
Exclusion criteria	Other causes of pain such as inflammatory or autoimmune disorders, current primary psychiatric conditions, substance abuse, contraindications for rTMS. Concomitant treatment for pain and sleep were allowed, provided the dose administered had been stable for at least 1 month before enrolment and remained stable throughout the study
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Mean (SD): 48.5(10.5) years. Gender (M:F): 1:37. Ethnicity: Not reported
Further population details	Chronic widespread pain
Extra comments	Duration of pain 3.7(4.2) years
Indirectness of population	No indirectness
Interventions	(n=19) Intervention 1: Electrical Physical Modalities - Transcranial Magnetic Stimulation (TMS). 14 sessions over 10 weeks (10 sessions over 2 weeks followed by maintenance phase of 4 sessions across 4 weeks). Duration 10 weeks. Concurrent medication/care: Not specified (n=19) Intervention 2: Placebo/Sham. Identical treatment but with a sham coil, that emitted a similar sound to

	the active coil. Duration 10 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Academic or government funding (Funding from Inserm and AP-HM)

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

Protocol outcome 1: Quality of life
- Actual outcome: SF-36 physical component summary score at 10 weeks; Group 1: mean 1.4 (SD 9); n=16, Group 2: mean 0.4 (SD 4.8); n=13; SF-36 0-100 Top=High is good outcome; Comments: Baseline: 29.9(7.5); 32.4(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: 3, Reason: NR; Group 2 Number missing: 6, Reason: NR
- Actual outcome: SF-36 mental component summary score at 10 weeks; Group 1: mean 5 (SD 6.9); n=16, Group 2: mean -1.6 (SD 7.6); n=13; SF-36 0-100 Top=High is good outcome; Comments: Baseline:39.6(11.4);34(9.3)
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: 3, Reason: NR; Group 2 Number missing: 6, Reason: NR

Protocol outcome 2: Psychological distress
- Actual outcome: BDI at 10 weeks; Group 1: mean -1.9 (SD 2.8); n=16, Group 2: mean -0.1 (SD 4.4); n=16; BDI Not reported Top=High is poor outcome
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: 3, Reason: NR; Group 2 Number missing: 6, Reason: NR
- Actual outcome: HADS anxiety at 10 weeks; Group 1: mean 0.4 (SD 1.7); n=16, Group 2: mean 0.5 (SD 2.3); n=13; HADS:A Not reported Top=High is poor outcome
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: 3, Reason: NR; Group 2 Number missing: 6, Reason: NR

Protocol outcomes not reported by the study	Pain reduction ; Physical function ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

Study	**Brietzke 2019** [54]
Study type	RCT (Patient randomised; Parallel)

Number of studies (number of participants)	(n=20)
Countries and setting	Conducted in Brazil; Setting: Not specified
Line of therapy	Unclear
Duration of study	Intervention time: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of fibromyalgia (ACR 2011 criteria)
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosis of fibromyalgia according to diagnostic criteria, daily disability present for the routine activities during the 3 months preceding enrolment, a score of at least 50mm on VAS 0-100mm.
Exclusion criteria	Contra-indications of the NIBS stimulation, positive history of other conditions such as rheumatoid arthritis, lupus autoimmune disease, neurological or oncological disease or cardiovascular disease.
Recruitment/selection of patients	2017-2018
Age, gender and ethnicity	Age - Mean (range):48.6 (18-59; 49.7(45-54) years. Gender (M:F): All female. Ethnicity: Not reported
Further population details	Chronic widespread pain
Extra comments	Mean duration of symptoms 5.75(1.48); 6.62(1.64)
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: Electrical Physical Modalities – TDCS The anodal electrode was used over the left DLPFC and the cathode at the right DLPFC. Current applied at 2mA for 30 minutes for 5 consecutive days for 12 weeks. Current was delivered using 35cm2 electrodes coated with a vegetable sponge, which was moistened with saline solution before the start of the stimulation by 2 silicone cannulas coupled to the electrode. Neoprene caps were produced in small, medium and large sizes and cap size selected appropriately for each patients head. The electrode position was then accurate for the subjects to facilitate the identification and avoid incorrect placement of the electrodes, the anode was painted red and cathode black (although equipment already set up – participant could not change any part of it). Duration 3 months. Concurrent medication/care: Not specified (n=10) Intervention 2: Placebo/Sham. Identical treatment but the electrical stimulation was not applied in the

	sham group. Duration 3 months. Concurrent medication/care: Not specified
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TDCS versus PLACEBO/SHAM Protocol outcome 1: Psychological distress - Actual outcome: BDI at 3 months; Group 1: mean 11.8 (SD 5.63); n=10, Group 2: mean 21.5 (SD 6.6); n=10; BDI 0-61 Top=High is poor outcome; Comments: Baseline: 27.1(12.1); 20.5(5.63) 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 Protocol outcome 1: Sleep - Actual outcome: Pittsburgh sleep quality index at 3 months; Group 1: mean 7.9 (SD 7.44); n=10, Group 2: mean 16.7 (SD 3.74); n=10; PSQI, range not reported, Top=High is poor outcome; Comments: Baseline: 27.5(7.63); 24.6(7.57) 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	
Protocol outcomes not reported by the study	Quality of life; Pain reduction; Physical function ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Discontinuation

Study	Carretero 2009[61]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=26)
Countries and setting	Conducted in Spain; Setting: Trial part of wider project investigating the usefulness of LF-RTMS in major depression being carried out by Hospital Son Llatzer, Hospital Son Dureta, and the University of the Balearic Islands, Majorca.
Line of therapy	Unclear
Duration of study	Intervention + follow up: 4 weeks + 8 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Fibromyalgia diagnosed by a rheumatologist according to the criteria of the American College of Rheumatology
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Over 18 and fulfilling the diagnostic criteria for major depression (Diagnostic and Statistical Manual of Mental Disorders-IV Text Revision) and fibromyalgia (criteria of the American College of Rheumatology).
Exclusion criteria	Not stated
Age, gender and ethnicity	Age - Mean (SD): Real TMS group 47.5 (5.7) ; Sham TMS group 54.9 (4.9). Gender (M:F): 2/24. Ethnicity: Not stated
Further population details	Chronic widespread pain
Extra comments	Duration of illness in participants not stated, but assumed from fibromyalgia diagnosis (≥ 3 months).
Indirectness of population	No indirectness
Interventions	(n=14) Intervention 1: Electrical Physical Modalities - Transcranial Magnetic Stimulation (TMS). High-frequency repetitive transcranial magnetic stimulation (HF-rTMS) using DANTEC TMS equipment (Dantec Medical, Medtronic Inc., Minneapolis, MN), MagLite model. A butterfly coil with each wing of 8.5 cm in diameter was used. Stimulation parameters were 20 trains at 110% of motor threshold for 60 seconds at 1 Hz and a 45-second interval between trains. A total of 1,200 pulses was administered at each of the 20 sessions, which each took approximately 30 minutes. The stimulation area was the right dorsolateral prefrontal area, 5 cm in front of the specular point that triggered a more selective right-thumb abduction response in the left motor cortex. Duration 4 weeks (20 sessions). Concurrent medication/care: Pharmacologic therapy remained

	unchanged during the month before the study and during the study. (n=12) Intervention 2: Placebo/Sham. In the sham sessions, the coil was placed perpendicularly to the cranium at the calculated stimulation point, before being inclined 45° forward on the axis. Thus, the magnetic field did not significantly penetrate the brain, although the patient did hear the sound produced by the apparatus. It was explained to patients that two randomly selected methods for applying magnetic fields were being used, and that the researchers wanted to know which one was more useful for people in their situation. Duration 4 weeks (10 sessions). Concurrent medication/care: Pharmacologic therapy remained unchanged during the month before the study and during the study.
Funding	Academic or government funding (IUNICS Institute, Universitat Illes Balears - grant SEJ2007-62312 (MICINN-FEDER Funds))
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCRANIAL MAGNETIC STIMULATION (TMS) versus PLACEBO/SHAM Protocol outcome 1: Pain reduction - Actual outcome: Pain reduction (Likert pain scale) at 3 months; Group 1: mean 8.1 (SD 1); n=14, Group 2: mean 7.5 (SD 2.1); n=12; Likert pain scale 0-10 Top=High is poor outcome; Comments: Baselines, mean (SD): Real TMS group 8.7 (1.2) Sham TMS group 8.6 (1.9) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: Small variation in continued background psychopharmacological therapy between patients; Group 1 Number missing: 1, Reason: Did not complete the treatment cycle. Group 2 Number missing: 1, Reason: Did not complete the treatment cycle.	
Protocol outcomes not reported by the study	Quality of life ; Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

Study	Chow 2004[77]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=20)
Countries and setting	Conducted in Australia; Setting: Not specified
Line of therapy	Unclear
Duration of study	Intervention + follow up: 7 week intervention and 3 months follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of chronic neck pain
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Over 18 years old, chronic neck pain, not experienced previous treatment with laser therapy other than laser acupuncture.
Exclusion criteria	Work related or third party injuries in which litigation or compensation was still current, abnormal neurological signs, inability to discontinue activity that exacerbated pain, conditions that could limit effectiveness of laser therapy or cause pain.
Recruitment/selection of patients	Adverts in the practice of the principle author
Age, gender and ethnicity	Age - Mean (SD): 57.7(10.9) years. Gender (M:F): 4:16. Ethnicity: Not specified
Further population details	Chronic primary musculoskeletal pain
Extra comments	Mean duration of pain 13.3 years (SE 2.48)
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: Electrical Physical Modalities - Laser therapy. 830nm laser therapy for 7 weeks. Diolase device, 15mm length laser and 3mm width at widest, 300mW power. Laser applied for 30s per point or until the area became less tender. 30 minute sessions. Duration 7 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=10) Intervention 2: Placebo/Sham. Identical treatment but laser did not emit a beam. Duration 7 weeks.

	Concurrent medication/care: Not specified. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LASER THERAPY versus PLACEBO/SHAM Protocol outcome 1: Quality of life - Actual outcome: SF-36 physical component summary score at 3 months (including 7 week intervention); Group 1: mean 4 (SD 8.22); n=10, Group 2: mean 1.22 (SD 6.32); n=10; SF-36 0-100 Top=High is good outcome; Comments: Baseline mean (SEs): 39(3.6); 41.6(3) SDs calculated from SDs reported in the study Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: NA, Reason: NR; Group 2 Number missing: NA, Reason: NR - Actual outcome: SF-36 mental component summary score at 3 months (including 7 week intervention); Group 1: mean 1.71 (SD 3.79); n=10, Group 2: mean 0 (SD 6.01); n=10; SF-36 0-100 Top=High is good outcome; Comments: Baseline mean (SEs): 50.9(3.4);50.1(2.5) SDs calculated from SDs reported in the study Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: NA, Reason: NR; Group 2 Number missing: NA, Reason: NR Protocol outcome 2: Pain reduction - Actual outcome: VAS at 3 months (including 7 week intervention); Group 1: mean 2.1 (SD 2.84); n=10, Group 2: mean 0.7 (SD 1.58); n=10; VAS 0-10 Top=High is poor outcome; Comments: Baseline mean (SEs): 3.9(0.6); 3.2(0.5) SDs calculated from SDs reported in the study Note: change scores in study transformed to scale whereby high score is good outcome. Converted back to high score = poor outcome in the analysis Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: NA, Reason: NR; Group 2 Number missing: NA, Reason: NR	
Protocol outcomes not reported by the study	Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

Study	Chow 2006[78]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=90)
Countries and setting	Conducted in Australia; Setting: Large suburban medical centre of 17 GPs in Sydney, Australia
Line of therapy	Unclear
Duration of study	Intervention + follow up: 7 week intervention and 12 week follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Chronic neck pain with unknown cause
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	18 years and over, pain for at least 3 months
Exclusion criteria	Injury with current compensation or litigation, abnormal neurological signs in the upper limbs due to nerve abnormalities, unable to discontinue activities that exacerbate pain, pregnancy, previous surgery on the cervical spine, RA, neck pain part of a widespread pain syndrome involving other areas, known photosensitivity or illnesses unrelated to neck pain which precluded involvement in study.
Recruitment/selection of patients	2002-2003, Posters in waiting room of medical centre and local newspaper adverts.
Age, gender and ethnicity	Age - Mean (SD): 56(12.8) years. Gender (M:F): 31:59. Ethnicity: Not specified
Further population details	Chronic primary musculoskeletal pain
Extra comments	Duration of pain 15(12.6) years
Indirectness of population	No indirectness
Interventions	(n=45) Intervention 1: Electrical Physical Modalities - Laser therapy. Diolase laser devices. 7 week intervention 1 session per week. Subjects treated with laser 15mm in length and 3mm at widest with a wavelength of 830nm and power of 300mW. Subjects seated comfortably and tender points in the next were identified, and each treated for 30 seconds per point with up to 50 points being treated within the maximum half-hour allocated for treatment. Number of points dependent on severity of symptoms. Duration 7 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness

	(n=45) Intervention 2: Placebo/Sham. Sham laser therapy. Digital display of machine on and sound emitted identical to active intervention, but device did not emit laser. Duration 7 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness
Funding	Funding not stated

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

Protocol outcome 1: Quality of life
- Actual outcome: SF-36 physical component summary score at 3 months (follow up); Group 1: mean 3.2 (SD 10.78); n=45, Group 2: mean 1.3 (SD 4.28); n=45; SF-36 summary score 0-100 Top=High is good outcome; Comments: Baseline not reported
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness; Group 1 Number missing: 2, Reason: Family illness; Group 2 Number missing: 3, Reason: Family illness, asthma requiring steroid treatment, unanticipated work changes
- Actual outcome: SF-36 mental component summary score at 3 months (follow up); Group 1: mean 2.4 (SD 8.99); n=45, Group 2: mean 5.4 (SD 10.98); n=45; SF-36 summary score 0-100 Top=High is good outcome; Comments: Baseline not reported
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness; Group 1 Number missing: 2, Reason: Family illness; Group 2 Number missing: 3, Reason: Family illness, asthma requiring steroid treatment, unanticipated work changes

Protocol outcome 2: Pain reduction
- Actual outcome: VAS at 3 months (follow up); Group 1: mean -2.7 (SD 1.99); n=45, Group 2: mean 0.3 (SD 2.33); n=45,
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: 2, Reason: Family illness; Group 2 Number missing: 3, Reason: Family illness, asthma requiring steroid treatment, unanticipated work changes

Protocol outcome 3: Discontinuation
- Actual outcome: Discontinuation of study at 3 months (follow up); Group 1: 2/45, Group 2: 3/45
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness; Group 1 Number missing: 2, Reason: Family illness; Group 2 Number missing: 3, Reason: Family illness, asthma requiring steroid treatment, unanticipated work changes

Protocol outcomes not reported by the study	Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep

Study	Da cunha 2008[92]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Brazil; Setting: Center of Occlusion and Temporomandibular Disorder of the Dental School of Sao Paulo State University (UNESP), Sao Jose dos Campos.
Line of therapy	Unclear
Duration of study	Intervention time: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Temporomandibular disorder diagnosed based on complete clinical examination, including patient's history, at the Center of Occlusion and Temporomandibular Disorder of the Dental School of Sao Paulo State University (UNESP).
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Sample selection was done based on complete clinical examination, including patients' history, masticatory and cervical muscle palpation, joint palpation and joint noises.
Exclusion criteria	Patients presenting asymptomatic joint clicking, major psychological problems, heart disease, psoriasis, rheumatoid arthritis, pregnancy and patients with pacemakers were not included in this study. Patients presenting myofascial trigger points and fibromyalgia were also excluded because of the particular characteristics of these entities.
Recruitment/selection of patients	One hundred and twenty patients were selected for assessment on a voluntary basis from a waiting list of those who presented for diagnosis and treatment of temporomandibular disorder.
Age, gender and ethnicity	Age - Mean: Laser group 40.15 years; Placebo group 46.6. Gender (M:F): 1/39. Ethnicity: Not stated
Further population details	1. Chronic orofacial pain
Extra comments	Before participating in this study, the selected patients had been waiting for treatment for at least six months, without any form of professional care.
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Electrical Physical Modalities - Laser therapy. The experimental group received laser treatment performed with a Ga-Al-As (Gallium-Aluminium-Arsenide) low level laser (Biolux laser - Bio-Art, Sao

	Carlos, SP, Brazil) from a probe applied perpendicularly and directly over the painful area. Duration 4 weeks. Concurrent medication/care: Patients had not received treatment or any professional care for 6 months prior to trial. Indirectness: No indirectness (n=20) Intervention 2: Placebo/Sham. The control group received a placebo treatment performed exactly in the same manner, but without energy output. Duration 4 weeks. Concurrent medication/care: Patients had not received treatment or any professional care for 6 months prior to trial. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LASER THERAPY versus PLACEBO/SHAM Protocol outcome 1: Pain reduction - Actual outcome: Level of pain (VAS) at 4 weeks (end of treatment); Group 1: mean 3.62 Visual analogue scale (VAS) (SD 2.45); n=20, Group 2: mean 4.67 Visual analogue scale (VAS) (SD 1.9); n=20; Visual analogue scale (VAS) 0-10 Top=High is poor outcome; Comments: Baselines, mean (SD): Laser group 6.87 (2.12) Placebo group 6.60 (2.57) 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 ; Baseline details: Mean pain baseline on VAS comparable between treatment and placebo groups.	
Protocol outcomes not reported by the study	Quality of life ; Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

Study (subsidiary papers)	Dailey 2019[94] (Dailey 2020[95])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=301)
Countries and setting	Conducted in USA; Setting: dual-site: University and University Medical Center
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: met ACR criteria for FM
Stratum	Overall: NA
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	female sex, age 18–70 years, FM according to the American College of Rheumatology 1990 criteria, on a stable medication regimen during the 4 weeks preceding the study, and projected to be on a stable treatment regimen for the next 2 months
Exclusion criteria	pain level of <4 on a 10-point numerical rating scale (NRS) at the first and second visits, inability to walk 6 minutes without assistance, TENS use in the last 5 years, presence of a pacemaker, history of neuropathic or autoimmune disorder, history of spinal fusion or metal implants in the spine, allergy to adhesive or nickel, pregnancy, epilepsy, and/or a serious or unstable medical or psychiatric condition that would preclude participation
Recruitment/selection of patients	recruited from the Pain Clinic, Rheumatology Clinic, Family Practice Clinic, Orthopedic Clinic, local physician offices, support groups, local physical therapy clinics, and radio and TV interviews, also from UIHC EPIC database for individuals with a diagnosis of myalgia and ResearchMatch (www.researchmatch.org). Specific recruitment strategies included mass email, posting flyers, and discussion of the project with physicians and nurses.

Age, gender and ethnicity	Age - Mean (SD): active: 44.7 (14.3), placebo: 47.2 (12.6), no TENS: 48.6 (11.8). Gender (M:F): all female . Ethnicity: White: active 92%, placebo 92%, no TENS 92%; not Hispanic: active 95%, placebo 95%, no TENS 95%
Further population details	1. Chronic orofacial pain: Pain other than chronic orofacial pain 2. Chronic primary musculoskeletal pain: Pain other than chronic primary musculoskeletal pain 3. Chronic visceral pain: Pain other than chronic visceral pain 4. Chronic widespread pain: Chronic widespread pain 5. Cognitive impairment: Not stated / Unclear 6. Complex regional pain syndrome: Pain other than complex regional pain syndrome 7. First language not English: Not stated / Unclear 8. Homeless: Not stated / Unclear 9. Learning difficulties: Not stated / Unclear 10. Sensory impairment : Not stated / Unclear
Extra comments	Duration of fibromyalgia, median (range) years: active 7 (3–12), placebo 7 (2–14), no TENS 7 (4–15)
Indirectness of population	No indirectness: NA
Interventions	(n=103) Intervention 1: Electrical Physical Modalities - Transcutaneous Electrical Nerve Stimulation (TENS). EMPI-Select TENS (DJO Global, Vista, CA) delivered through butterfly electrodes placed at the cervicothoracic junction and lower back. Active-TENS parameters were asymmetrical, biphasic waveform with a modulating frequency (2-125 Hz), pulse duration 200u sec, and highest tolerable stimulation intensity. TENS was applied by the TENS-Allocator in the clinic for 30 min prior to the Outcome-Assessor measuring effects on pain, fatigue, and function. Following completion of Visit-2, active-TENS was sent home with participants with an instruction manual developed by study personnel. TENS-Allocators used a standardized script to instruct participants in home use and for weekly contact. Participants were instructed to use TENS at least 2h per day during activity. TENS units monitored number of sessions, number of minutes used, and average intensity per channel. Duration 4 weeks. Concurrent medication/care: All participants continued current treatments prescribed by their health care provider and were asked not to change medications during the study. . Indirectness: No indirectness; Indirectness comment: NA (n=99) Intervention 2: Placebo/Sham. EMPI-Select TENS (DJO Global, Vista, CA) delivered through butterfly electrodes placed at the cervicothoracic junction and lower back. TENS was applied by the TENS-Allocator in the clinic for 30 min prior to the Outcome-Assessor measuring effects on pain, fatigue, and function. The placebo-TENS unit delivered current for 45s ramping down to 0 in the last 15s and the appearance was identical to the active unit. Following completion of Visit-2 placebo-TENS was sent home with participants with an instruction manual developed by study personnel.

	TENS-Allocators used a standardized script to instruct participants in home use and for weekly contact. Participants were instructed to use TENS at least 2h per day during activity. Placebo-TENS units monitored number of sessions, number of minutes used, and average intensity per channel. Duration 4 weeks . Concurrent medication/care: All participants continued current treatments prescribed by their health care provider and were asked not to change medications during the study.. Indirectness: No indirectness; Indirectness comment: NA (n=99) Intervention 3: Usual care. No TENS - used a mock-TENS during visits to blind Outcome-Assessors with electrodes that were attached to a TENS unit that provided no current intensity Duration 4 weeks . Concurrent medication/care: All participants continued current treatments prescribed by their health care provider and were asked not to change medications during the study. Indirectness: No indirectness; Indirectness comment: NA
Funding	Academic or government funding (NIH. One author received consulting fees from pharmaceutical companies. Active and placebo TENS units and electrodes were provided by DJO, Inc.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION (TENS) versus PLACEBO/SHAM

Protocol outcome 1: Quality of life
- Actual outcome: SF36 mental composite at 4 weeks ; MD; 1.1 (95%CI -1.9 to 4.1) (p value : >0.99) T score SF36 0-100 Top=High is good outcome, Comments: Mean difference in T scores, adjusted for study site differences at baseline. Baseline values: TENS 88.7 (10), placebo 40.2 (10.2);
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: difference in marital status and FIQR, but model adjusted for baseline differences ; Group 1 Number missing: 18, Reason: unclear ; Group 2 Number missing: 18, Reason: unclear
- Actual outcome: SF36 physical composite at 4 weeks ; MD; 1.2 (95%CI -0.7 to 3.1) (p value : 0.36) T scores SF36 0-100 Top=High is good outcome, Comments: Mean difference in T scores, adjusted for study site differences at baseline. Baseline values: TENS 32.7 (6.4), placebo 33.3 (6.2)
;
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: difference in marital status and FIQR, but model adjusted for baseline differences ; Group 1 Number missing: 18, Reason: unclear ; Group 2 Number missing: 18, Reason: unclear

Protocol outcome 2: Pain reduction
- Actual outcome: Brief pain inventory - intensity at 4 weeks ; MD; -0.5 (95%CI -1 to 0) (p value : 0.036) BPI intensity 0-10 Top=High is poor outcome, Comments: Adjusted for study site differences at baseline. Baseline values: not reported ;

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, Comments: NA; Baseline details: difference in marital status and FIQR, but model adjusted for baseline differences. Outcome values at baseline not reported ; Group 1 Number missing: 18, Reason: unclear ; Group 2 Number missing: 18, Reason: unclear

Protocol outcome 3: Physical function
- Actual outcome: 6 minute walk test at 4 weeks ; MD; 19 (95%CI -58 to 96) (p value : >0.99) number of feet walked , Comments: adjusted for study site differences at baseline. Baseline values: TENS 1386 (323), placebo 1358 (305);
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, Comments: NA; Baseline details: difference in marital status and FIQR, but model adjusted for baseline differences ; Group 1 Number missing: 18, Reason: unclear ; Group 2 Number missing: 18, Reason: unclear

Protocol outcome 4: Psychological distress
- Actual outcome: PROMIS depression at 4 weeks ; MD; -2.7 (95%CI -4.7 to -0.8) (p value : 0.002) T scores PROMIS depression 8-40 Top=High is poor outcome, Comments: Mean difference in T scores, adjusted for study site differences at baseline. Baseline values: TENS 58.1 (8.1), placebo 55.7 (8.5)
;
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: difference in marital status and FIQR, but model adjusted for baseline differences ; Group 1 Number missing: 18, Reason: unclear ; Group 2 Number missing: 18, Reason: unclear
- Actual outcome: PROMIS anxiety at 4 weeks ; MD; -0.5 (95%CI -2.7 to 1.7) (p value : >0.99) T scores PROMIS anxiety 7-35 Top=High is poor outcome, Comments: Mean difference in T scores, adjusted for study site differences at baseline. Baseline values: TENS 58.8 (8.7), placebo 58.1 (8)
;
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: difference in marital status and FIQR, but model adjusted for baseline differences ; Group 1 Number missing: 18, Reason: unclear ; Group 2 Number missing: 18, Reason: unclear

Protocol outcome 5: Pain interference
- Actual outcome: Brief pain inventory - interference at 4 weeks ; MD; -0.7 (95%CI -1.3 to 0.01) (p value : 0.043) NA BPI interference 0-10 Top=High is poor outcome, Comments: adjusted for study site differences at baseline. Baseline values: not reported ;
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, Comments: NA; Baseline details: difference in marital status and FIQR, but model adjusted for baseline differences. Outcome values at baseline not reported ; Group 1 Number missing: 18, Reason: unclear ; Group 2 Number missing: 18, Reason: unclear

Protocol outcome 6: Pain self-efficacy
- Actual outcome: Pain self-efficacy questionnaire at 4 weeks ; MD; 1.6 (95%CI -1.8 to 5.1) (p value : 0.75) NA Pain self-efficacy questionnaire 0-

60 Top=High is good outcome, Comments: adjusted for study site differences at baseline. Baseline values: TENS 28.2 (13.3), placebo 29.9 (13.1)
;
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, Comments: NA; Baseline details: difference in marital status and FIQR, but model adjusted for baseline differences ; Group 1 Number missing: 18, Reason: unclear ; Group 2 Number missing: 18, Reason: unclear

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION (TENS) versus USUAL CARE

Protocol outcome 1: Quality of life
- Actual outcome: SF36 mental composite at 4 weeks ; MD; 2.4 (95%CI -0.6 to 5.3) (p value : 0.17) T scores SF36 0-100 Top=High is good outcome, Comments: mean difference in T scores, adjusted for study site differences at baseline. Baseline values: TENS 38.7 (10), no TENS 39.5 (10.6)
;
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: difference in marital status and FIQR, but model adjusted for baseline differences ; Group 1 Number missing: 18, Reason: unclear ; Group 2 Number missing: 8, Reason: unclear
- Actual outcome: SF36 physical composite at 4 weeks ; MD; 1 (95%CI -0.8 to 2.8) (p value : 0.58) T scores SF36 0-100 Top=High is good outcome, Comments: mean difference in T scores, adjusted for study site differences at baseline. Baseline values: TENS 32.7 (6.4), no TENS 32.7 (6.6)
;
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: difference in marital status and FIQR, but model adjusted for baseline differences ; Group 1 Number missing: 18, Reason: unclear ; Group 2 Number missing: 8, Reason: unclear

Protocol outcome 2: Pain reduction
- Actual outcome: Brief pain inventory - intensity at 4 weeks ; MD; -0.9 (95%CI -1.4 to -0.4) (p value : <0.0001) BPI intensity 0-10 Top=High is poor outcome, Comments: adjusted for study site differences at baseline. Baseline values: not reported ;
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, Comments: NA; Baseline details: difference in marital status and FIQR, but model adjusted for baseline differences. Baseline outcome values not reported ; Group 1 Number missing: 18, Reason: unclear ; Group 2 Number missing: 8, Reason: unclear

Protocol outcome 3: Physical function
- Actual outcome: 6 minute walk test at 4 weeks ; MD; 42 (95%CI -34 to 117) (p value : >0.99) number of feet walked , Comments: adjusted for study site differences at baseline. Baseline values: TENS 1386 (323), no TENS 1316 (318)
;
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, Comments: NA; Baseline details: difference in marital status and FIQR, but model adjusted for baseline differences ; Group 1 Number missing: 18, Reason: unclear ; Group 2 Number missing: 8, Reason: unclear Protocol outcome 4: Psychological distress - Actual outcome: PROMIS depression at 4 weeks ; MD; -3.2 (95%CI -5.1 to -1.3) (p value : 0.0001) T scores PROMIS depression 8-40 Top=High is poor outcome, Comments: mean difference in T scores, adjusted for study site differences at baseline. Baseline values: TENS 58.1 (8.1), no TENS 56.6 (8.1) ; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: difference in marital status and FIQR, but model adjusted for baseline differences ; Group 1 Number missing: 18, Reason: unclear ; Group 2 Number missing: 8, Reason: unclear - Actual outcome: PROMIS anxiety at 4 weeks ; MD; -0.4 (95%CI -2.5 to 1.7) (p value : >0.99) T scores , Comments: mean difference in T scores, adjusted for study site differences at baseline. Baseline values: TENS 58.8 (8.7), no TENS 58.3 (7.8) ; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: difference in marital status and FIQR, but model adjusted for baseline differences ; Group 1 Number missing: 18, Reason: unclear ; Group 2 Number missing: 8, Reason: unclear Protocol outcome 5: Pain interference - Actual outcome: Brief pain inventory - interference at 4 weeks ; MD; -0.6 (95%CI -1.3 to 0) (p value : 0.048) BPI interference 0-10 Top=High is poor outcome, Comments: adjusted for study site differences at baseline. Baseline values: not reported ; 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, Comments: NA; Baseline details: difference in marital status and FIQR, but model adjusted for baseline differences. Baseline outcome values not reported ; Group 1 Number missing: 18, Reason: unclear ; Group 2 Number missing: 8, Reason: unclear Protocol outcome 6: Pain self-efficacy - Actual outcome: Pain self-efficacy questionnaire at 4 weeks ; MD; 2.3 (95%CI -1 to 5.7) (p value : 0.28) Pain self-efficacy questionnaire 0-60 Top=High is good outcome, Comments: adjusted for study site differences at baseline. Baseline values: TENS 28.2 (13.3), no TENS 29 (13.2) ; 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, Comments: NA; Baseline details: difference in marital status and FIQR, but model adjusted for baseline differences ; Group 1 Number missing: 18, Reason: unclear ; Group 2 Number missing: 8, Reason: unclear	
Protocol outcomes not reported by the study	Use of healthcare services; Sleep; Discontinuation

Study	Dall'agnol 2014[96]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=24)
Countries and setting	Conducted in Brazil
Line of therapy	Unclear
Duration of study	Intervention + follow up: 10 rTMS sessions + 3 months follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Myofascial pain syndrome was diagnosed by two independent examiners with more than 10 years of clinical experience related to chronic pain.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Right-handed females aged 19 to 65 years with a diagnosis of myofascial pain syndrome in an upper body segment for at least 3 months prior to enrolment. Participants were also required to be experiencing limitation in at least one of the following areas of life: work, personal relationships, pleasure of activities, responsibilities at home, personal goals, clear thinking. MPS as defined by regional pain, normal neurologic examination, decreased range of motion, stiffness in the muscles, presence of trigger points, taut bands, tender points, palpable nodules, and pain characterized by dull, hollow, or deep that was exacerbated during stress. Must have scored ≥ 4 on the Neuropathic Pain Diagnostic Questionnaire.
Exclusion criteria	Presence of any other pain disorder, such as rheumatoid arthritis, radiculopathy, and fibromyalgia;
Age, gender and ethnicity	Age: mean (SD): 45.43(12.86) years . Gender (M:F): 0:24. Ethnicity: Not stated
Further population details	Chronic primary musculoskeletal pain
Indirectness of population	No indirectness
Interventions	(n=12) Intervention 1: Electrical Physical Modalities - Transcranial Magnetic Stimulation (TMS). TMS performed with a MagPro X100 and a figure-8 coil. The hot spot was marked on the scalp with a soft-tip pen. The subjects were comfortably seated in a reclining chair with arm rests for relaxing arms and hand positioning. The coil was placed over the left motor cortex (M1), held tangentially to the scalp with the handle pointing back and away from the midline at 45 degrees. All participants underwent rTMS delivered in trains consisting of 16 series of 10-second pulses with a high frequency of 10 Hz of biphasic magnetic stimulator (MagPro X100) and an interval of 26 seconds between each train, giving a total of 1,600 pulses per session. The stimulation intensity used was 80% of resting motor threshold (RMT). Duration 10 sessions. Concurrent

	medication/care: All of the patients were permitted to use supplementary analgesic medication (acetaminophen, ibuprofen, codeine, or tramadol) to relieve their pain if necessary. Patients were allowed to take 750mgof acetaminophen up to 4 times per day and 200 mg of ibuprofen at maximum 4 times per day as a rescue analgesic. If these drugs were ineffective, patients could use Dorflex (Sanofi Aventis, Sao Paulo, Brazil; 35 mg orphenadrine citrate combined with 300 mg dipyrone and 50 mg caffeine). If their pain persisted, patients were permitted to use 60mgof codeine up to 4 times per day or tramadol 3 times per day. The patients were asked to record their analgesic intake during the treatment period in their pain diaries, and these diaries were reviewed during each intervention session. The total analgesic dose administered during treatment was considered for the analysis. Indirectness: No indirectness (n=12) Intervention 2: Placebo/Sham. During placebo (sham stimulation), an inactive rTMS coil (MagPro X100) was used as a sham coil and was placed in the identical area as the active coil. The patient recorded identical experiences (including sound effects and somatic sensations caused by contraction of the muscles of the scalp) as during active stimulation. Duration 10 sessions. Concurrent medication/care: All of the patients were permitted to use supplementary analgesic medication (acetaminophen, ibuprofen, codeine, or tramadol) to relieve their pain if necessary. Patients were allowed to take 750mgof acetaminophen up to 4 times per day and 200 mg of ibuprofen at maximum 4 times per day as a rescue analgesic. If these drugs were ineffective, patients could use Dorflex (Sanofi Aventis, Sao Paulo, Brazil; 35 mg orphenadrine citrate combined with 300 mg dipyrone and 50 mg caffeine). If their pain persisted, patients were permitted to use 60mgof codeine up to 4 times per day or tramadol 3 times per day. The patients were asked to record their analgesic intake during the treatment period in their pain diaries, and these diaries were reviewed during each intervention session. The total analgesic dose administered during treatment was considered for the analysis. Indirectness: No indirectness
Funding	Academic or government funding (Grants and material from the Brazilian Innovation Agency, Committee for the Development of Higher Education Personnel, National Council for Scientific and Technological Development, Postgraduate Program in Medical Sciences at the School of Medicine of the Federal University of Rio Grande do Sul, Postgraduate Research Group at the Hospital de Clinicas de Porto Alegre and the Foundation for Support of Research at Rio Grande do Sul.)

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

Protocol outcome 1: Pain reduction
- Actual outcome: Pain intensity (visual analogue scale) at 3 months after treatment; Group 1: mean 3.57 Pain reported on VAS (SD 2.82); n=12, Group 2: mean 5.29 Pain reported on VAS (SD 2.78); n=12; VAS 0-10 Top=High is poor outcome; Comments: Baselines, mean (SD):
Placebo 6.83 (2.45)

rTMS 6.94 (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, Other 1 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Treatment inefficacy.; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

Study	**Del vecchio 2019[101]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=60)
Countries and setting	Conducted in Italy; Setting: Department of Dental Sciences and Maxillo-Facial Surgery of Sapienza, University of Rome
Line of therapy	Unclear
Duration of study	Intervention time: 1 week

Method of assessment of guideline condition	Adequate method of assessment/diagnosis: TMJD diagnosis. The disorder was diagnosed by clinical and radiological examinations and according to the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD)Axis I and Axis II
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	The inclusion criteria to been rolled in the study were: the presence of pain in the joint area and/or radiating to the face, jaw, or neck for at least six months; reduced mouth opening or jaw locks; painful clicking, popping or grating when opening or closing the mouth; occlusal changes; no muscle tenderness at palpation; and no drug consumption for at least three weeks before treatment.
Exclusion criteria	None specified
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Mean (SD): 42.55 (14.842) years. Gender (M:F): 12:74. Ethnicity: Not specified
Further population details	Chronic orofacial pain
Extra comments	Duration of pain not specified (minimum duration 6 months)
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Electrical Physical Modalities - Laser therapy. Received LLLT through the B-cureDental Pro low-level laser device, provided by BiocareEnterprise Limited (Good Energies, Haifa, Israel). This medical device emits a low-level laser beam with a wavelength of 808 nm; each application was performed at 5 J/min, 250 mW and 15 KHz for 8 m, for a total of40J each, directly over the pain area. The treatment had to be performed twice a day for seven consecutive days. A laser therapy expert examiner performed the first application at the Department of Dental Sciences and Maxillo-Facial Surgery of Sapienza, University of Rome. This first application was used as an instruction to the patients so they could perform the successive applications by themselves at home. The same examiner explained clearly to each patient how to use and safely store the devices. After the instruction, each patient performed the remaining applications at home. Duration 1 week. Concurrent medication/care: Not specified. Indirectness: No indirectness (n=30) Intervention 2: Placebo/Sham. Participants received the same instructions and followed the same protocol as the SG patients but received a sham laser device manufactured also by Biocare Enterprise Limited (Good Energies, Haifa,Israel) with the same exterior characteristics of the effective device, including the guide beam and the working sound, but devoid of the therapeutic diode source. Duration 1 week. Concurrent medication/care: Not specified. Indirectness: No indirectness

Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LASER THERAPY versus PLACEBO/SHAM Protocol outcome 1: Pain reduction - Actual outcome: VAS pain reduction at 1 week; Group 1: mean 35.17 (SD 22.139); n=29, Group 2: mean 22.14 (SD 16.635); n=28; VAS 0-100 Top=High is poor outcome 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 ; Baseline details: Minimal baseline details; Group 1 Number missing: 1; Group 2 Number missing: 2	
Protocol outcomes not reported by the study	Quality of life ; Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

Study	Esenyel 2000[117]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=76)
Countries and setting	Conducted in Turkey; Setting: Not specified
Line of therapy	Unclear
Duration of study	Intervention time: 10 days (with 12 week follow up)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of myofascial pain
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Travel and Simons criteria for active myofascial trigger points in the upper trapezius muscle.
Exclusion criteria	Meeting the ACR criteria for fibromyalgia, having myofascial trigger point infections or receiving physical medicine in the year preceding this study, having a history of acute trauma, inflammatory joint or muscle disease, infection or malignancy, or evidence of neurologic deficit.
Recruitment/selection of patients	Consecutively recruited from the outpatient clinic of the physical medicine and rehab department and the pain clinic of a hospital over a 2.3 year period.
Age, gender and ethnicity	Age - Mean (SD): 30(7.7) years. Gender (M:F): 38:64. Ethnicity: Not stated
Further population details	Chronic widespread pain
Extra comments	Pain duration ranged 6 months to 7 years
Indirectness of population	No indirectness
Interventions	(n=36) Intervention 1: Electrical Physical Modalities - Therapeutic Ultrasound. Ultrasound therapy 1.5Wcm2 to trigger points for 6 minute duration for 10 sessions, as well as neck-stretching exercises. Duration 10 days. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=40) Intervention 2: Usual care. Neck stretching exercises only. Duration 10 days. Concurrent medication/care: Not reported. Indirectness: No indirectness

Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: THERAPEUTIC ULTRASOUND versus USUAL CARE Protocol outcome 1: Pain reduction - Actual outcome: VAS at 3 months; Group 1: mean 3.08 (SD 2.42); n=36, Group 2: mean 5.78 (SD 0.87); n=40; VAS 0-10 Top=High is poor outcome; Comments: Baseline not reported Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life ; Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

Study	Fagerlund 2015[120]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=50)
Countries and setting	Conducted in Norway; Setting: Pain clinic, university hospital of Northern Norway
Line of therapy	Unclear
Duration of study	Intervention + follow up: 5 day intervention and 1 month follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ACR criteria for fibromyalgia
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Over 18 years old, diagnosed with FMS, and manual examination of patients' tender points confirmed this. If on medication, this needed to be stable for 3 months before inclusion
Exclusion criteria	Severe psychiatric conditions, neurological conditions, developmental disorders, pregnancy and drug abuse.
Recruitment/selection of patients	Commenced September 2011, from Tromso (Northern Norway) - patients treated in pain clinics in the previous 2 years and members of the national FM patient association were contacted by mail, as well as advertisements in local newspapers
Age, gender and ethnicity	Age - Mean (SD): 48.6 (9.4) years. Gender (M:F):3:47. Ethnicity: Not specified
Further population details	Chronic widespread pain
Extra comments	Duration of pain 18.1(9) years
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Electrical Physical Modalities - Transcranial Direct Current Stimulation (TDCS). 5 consecutive days of treatment. Direct current stimulation administered using neuroConn DC stimulator. Stimulation duration 20 minutes, intensity of 2mA. Anodes placed at C3 position and cathode placed on contralateral supraorbital area. Duration 5 days. Concurrent medication/care: Not specified. Indirectness: No indirectness (n=25) Intervention 2: Placebo/Sham. Identical treatment but sham treatment; 8 second fade in period

	followed by 30 seconds of direct current stimulation that was terminated by a 5 second fade out (mimics skin sensation of active treatment with insufficient duration to induce changes in cortical excitability). Duration 5 days. Concurrent medication/care: Not specified. Indirectness: No indirectness
Funding	Funding not stated

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

Protocol outcome 1: Quality of life
- Actual outcome: SF-36 physical component at 1 month (follow up); Group 1: mean 34.78 (SD 9.42); n=24, Group 2: mean 35.92 (SD 7.34); n=24; SF-36 summary score 0-100 Top=High is good outcome; Comments: Baseline: 29.83(26.17-33.49); 34.55(31.37-37.74)

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 ; Baseline details: Difference at baseline more than MIDs; Group 1 Number missing: 1, Reason: NR; Group 2 Number missing: 1, Reason: NR
- Actual outcome: SF-36 mental component at 1 month (follow up); Group 1: mean 48.2 (SD 15.35); n=24, Group 2: mean 45.4 (SD 10.85); n=24; SF-36 summary score 0-100 Top=High is good outcome; Comments: Baseline: 48.16(42.54-53.78);45.88(39.92-51.83)

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 ; Baseline details: Difference at baseline more than MIDs; Group 1 Number missing: 1, Reason: NR; Group 2 Number missing: 1, Reason: NR

Protocol outcome 2: Pain reduction
- Actual outcome: Pain intensity (numeric rating scale) at 1 month (follow up); Group 1: mean 4.26 (SD 1.9); n=24, Group 2: mean 5.22 (SD 1.5); n=24; NRS 0-10 Top=High is poor outcome; Comments: Baseline: 4.93(1.58); 5.31(1.59)
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 ; Baseline details: Difference at baseline; Group 1 Number missing: 1, Reason: NR; Group 2 Number missing: 1, Reason: NR

Protocol outcome 3: Psychological distress
- Actual outcome: HADS anxiety at 1 month (follow up); Group 1: mean 5.47 (SD 4.16); n=24, Group 2: mean 5.82 (SD 3.36); n=24; HADS:A Not specified Top=High is poor outcome; Comments: Baseline: 6.9(3.99);6.48(3.48)
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 ; Baseline details: Difference at baseline; Group 1 Number missing: 1, Reason: NR; Group 2 Number missing: 1, Reason: NR

- Actual outcome: HADS depression at 1 month (follow up); Group 1: mean 3.76 (SD 2.77); n=24, Group 2: mean 5.41 (SD 3.37); n=24; HADS:D Not specified Top=High is poor outcome; Comments: Baseline: 5.33(3.04); 6.13(3.53) 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 ; Baseline details: Difference at baseline; Group 1 Number missing: 1, Reason: NR; Group 2 Number missing: 1, Reason: NR	
Protocol outcomes not reported by the study	Physical function ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

Study	Fregni 2006[129]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=32)
Countries and setting	Conducted in Brazil; Setting: Not specified
Line of therapy	Unclear
Duration of study	Intervention + follow up: 1 week (and 3 week follow up)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ACR criteria for fibromyalgia
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Met ACR criteria for FMS, score of at least 4 on VAS and at least 20 on the total tender point score. Participants were required to maintain a stable dose of any medications they were on.
Exclusion criteria	Uncontrolled clinical disease such as thyroid or cardiovascular disease, substance abuse, pregnancy, lactation
Recruitment/selection of patients	From a specialised outpatient centre
Age, gender and ethnicity	Age - Mean (SD): 53.2(8.97) years. Gender (M:F): All female. Ethnicity: Not specified
Further population details	Chronic widespread pain
Extra comments	Mean duration of pain 8.4(9.3) years
Indirectness of population	No indirectness
Interventions	(n=11) Intervention 1: Electrical Physical Modalities - Transcranial Direct Current Stimulation (TDCS). Current transferred by a pair of saline soaked surface sponge electrodes and battery driven stimulators with maximum output of 10mA. Anodal stimulation of left DLPFC area. Constant current of 2mA intensity was applied for 20 minutes. Duration 5 days. Concurrent medication/care: Not specified. Indirectness: No indirectness (n=11) Intervention 2: Electrical Physical Modalities - Transcranial Direct Current Stimulation (TDCS). Current transferred by a pair of saline soaked surface sponge electrodes and battery driven stimulators with maximum output of 10mA. Anodal stimulation of primary motor cortex area. Constant current of 2mA intensity was

	applied for 20 minutes. Duration 5 days. Concurrent medication/care: Not specified. Indirectness: No indirectness (n=10) Intervention 3: Placebo/Sham. Identical treatment with sham stimulation of the primary motor cortex. The stimulator was turned off after 30 seconds of stimulation. The patients therefore felt the initial itching sensation but received no current for the rest of the stimulation period. Duration 5 days. Concurrent medication/care: Not specified. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS) FOR DLPFC versus PLACEBO/SHAM Protocol outcome 1: Psychological distress - Actual outcome: BDI at 3 weeks; Group 1: mean 14.6 (SD 5.7); n=11, Group 2: mean 18 (SD 7.7); n=10; Comments: baseline:17.8(8.7); 20.7(8.1) 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 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS) FOR M1 versus PLACEBO/SHAM Protocol outcome 1: Psychological distress - Actual outcome: BDI at 3 weeks; Group 1: mean 18.6 (SD 9.1); n=11, Group 2: mean 18 (SD 7.7); n=10; BDI Not reported Top=High is poor outcome; Comments: Baseline: 19.9(8.2); 20.7(8.1) 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	
Protocol outcomes not reported by the study	Quality of life ; Pain reduction ; Physical function ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

Study	Gokyildiz 2012[137]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=26)
Countries and setting	Conducted in Turkey; Setting: Urogynecology Unit, Istanbul Medical School Department of Obstetrics and Gynecology, Istanbul University.
Line of therapy	Unclear
Duration of study	Intervention time: 3 months
Method of assessment of guideline condition	Method of assessment/diagnosis not stated: All the patients were evaluated through CPP history, physical examination, gynecological examination and ultrasound at Istanbul Medical School Department of Obstetrics and Gynecology, Istanbul University.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosis of CPP; voluntary participation; pain score >5 according to the visual analogue scale (VAS); cessation of analgesic at least 2 weeks before PTNS treatment; cessation of physiotherapy or electrotherapy at least 3 months before PTNS treatment.
Exclusion criteria	Pregnancy or planning a pregnancy; heart disease or cardiac pacing; nerve damage; use of anticoagulant medicine; active or recurrent urinary tract infection (more than five in the last 12 months).
Recruitment/selection of patients	8,872 gynecology patient records in the year 2006, 10,427 in the year 2007 and 500 in the year 2008 were reviewed at Istanbul Medical School Department of Obstetrics and Gynecology, Istanbul University. Sixty-five patients who had pain in the pelvis/lower abdomen for at least 6 months were identified and these patients were called and asked whether they still had pain. Those who still did were invited to the Urogynecology Unit and 52 patients applied to the unit.
Age, gender and ethnicity	Age - Other: Ages not stated, but report that 'no significant difference between the women in the control and experimental groups in terms of age'. Gender (M:F): 0/26. Ethnicity: Not stated
Further population details	Chronic visceral pain
Extra comments	Chronic population: pain in pelvis and lower abdomen for at least 6 months.
Indirectness of population	No indirectness

Interventions	(n=13) Intervention 1: Electrical Physical Modalities - Percutaneous Electrical Nerve Stimulation (PENS). Percutaneous Tibial Nerve Stimulation (PTNS) was applied using a neuromodulation system composing a needle set and a stimulator that runs with a 9-volt battery and creates an adjustable current between 0.5 and 10 mA, 200s and 20 Hz frequency. The patients lay on their backs in a supine position with the knees abducted and flexed (frog position). The 34-gauge needle was inserted approximately 3–4 cm above the inner malleolus, by entering at the place appropriate to the posterior tibial nerve line with a 60° angle, the adhesive electrode was placed on the inner side of the heel and the set was connected to the stimulator. The stimulator was run and the current was adjusted according to the patient's tolerance. When the current is flowing correctly, if the inserted needle is in the right place, toes should have plantar flexion (moving downwards) and/or 2nd to 5th fingers should release or have plantar flexion. Each session lasted 30 minutes. Duration 3 months (12 sessions). Concurrent medication/care: None. Inclusion required cessation of analgesic at least 2 weeks before treatment and cessation of physiotherapy or electrotherapy at least 3 months before treatment. Indirectness: No indirectness (n=13) Intervention 2: Usual care. Received 'routine intervention' (normal care) for 3 months. Duration 3 months. Concurrent medication/care: None. Inclusion required cessation of analgesic at least 2 weeks before treatment and cessation of physiotherapy or electrotherapy at least 3 months before treatment. Indirectness: No indirectness
Funding	Funding not stated (State no conflict of interest.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PERCUTANEOUS ELECTRICAL NERVE STIMULATION (PENS) versus USUAL CARE

Protocol outcome 1: Quality of life
- Actual outcome: SF-36 Physical function at After treatment (3 months); Group 1: mean 74.16 (SD 31.03); n=12, Group 2: mean 52.91 (SD 23.1); n=12; SF-36 0-100 Top=High is good outcome; Comments: Baselines, mean (SD):
PENS group 56.66 (23.19)
Control group 54.58 (23.88)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Key outcome baselines comparable between experimental and control groups. Differences in baseline for SF-36 Physical role and SF-36 Social functioning. ; Group 1 Number missing: 1, Reason: Unclear ("dropped"); Group 2 Number missing: 1, Reason: Unclear ("dropped")
- Actual outcome: SF-36 Physical role at After treatment (3 months); Group 1: mean 66.66 (SD 45.64); n=12, Group 2: mean 14.58 (SD 22.5); n=12; Sf-36 0-100 Top=High is good outcome; Comments: Baselines, mean (SD):
PENS group 25.00 (35.35)
Control group 12.5 (25.00)

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Key outcome baselines comparable between experimental and control groups. Differences in baseline for SF-36 Physical role and SF-36 Social functioning. ; Group 1 Number missing: 1, Reason: Unclear ("dropped"); Group 2 Number missing: 1, Reason: Unclear ("dropped")
- Actual outcome: SF-36 Emotional role at After treatment (3 months); Group 1: mean 61.11 (SD 44.57); n=12, Group 2: mean 13.87 (SD 26.4); n=12; SF-36 0-100 Top=High is good outcome; Comments: Baselines, mean (SD):
PENS group 27.77 (37.15)
Control group 19.42 (29.98)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Key outcome baselines comparable between experimental and control groups. Differences in baseline for SF-36 Physical role and SF-36 Social functioning. ; Group 1 Number missing: 1, Reason: Unclear ("dropped"); Group 2 Number missing: 1, Reason: Unclear ("dropped")
- Actual outcome: SF-36 Energy/fatigue at After treatment (3 months); Group 1: mean 62.91 (SD 25.97); n=12, Group 2: mean 45 (SD 16.23); n=12; SF-36 0-100 Top=High is good outcome; Comments: Baselines, mean (SD):
PENS group 49.16 (14.74)
Control group 46.25 (18.35)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Key outcome baselines comparable between experimental and control groups. Differences in baseline for SF-36 Physical role and SF-36 Social functioning. ; Group 1 Number missing: 1, Reason: Unclear ("dropped"); Group 2 Number missing: 1, Reason: Unclear ("dropped")
- Actual outcome: SF-36 Mental health at After treatment (3 months); Group 1: mean 60.66 (SD 19.35); n=12, Group 2: mean 40.33 (SD 15.48); n=12; SF-36 0-100 Top=High is good outcome; Comments: Baselines, mean (SD):
PENS group 42.00 (17.18)
Control group 42.33 (18.48)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Key outcome baselines comparable between experimental and control groups. Differences in baseline for SF-36 Physical role and SF-36 Social functioning. ; Group 1 Number missing: 1, Reason: Unclear ("dropped"); Group 2 Number missing: 1, Reason: Unclear ("dropped")
- Actual outcome: SF-36 Social functioning at After treatment (3 months); Group 1: mean 71.87 (SD 33.33); n=12, Group 2: mean 50 (SD 11.91); n=12; SF-36 0-100 Top=High is good outcome; Comments: Baselines, mean (SD):
PENS group 43.75 (25.28)
Control group 54.16 (17.94)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Key outcome baselines comparable between experimental and control groups. Differences in baseline for SF-36 Physical role and SF-36 Social functioning. ; Group 1 Number missing: 1, Reason: Unclear ("dropped"); Group 2 Number missing: 1, Reason: Unclear ("dropped")
- Actual outcome: SF-36 Pain at After treatment (3 months); Group 1: mean 60 (SD 27.96); n=12, Group 2: mean 23.33 (SD 7.78); n=12; SF-36 0-100 Top=High is good outcome; Comments: Baselines, mean (SD):

PENS group 32.5 (23.40) Control group 23.33 (7.78) Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Key outcome baselines comparable between experimental and control groups. Differences in baseline for SF-36 Physical role and SF-36 Social functioning. ; Group 1 Number missing: 1, Reason: Unclear ("dropped"); Group 2 Number missing: 1, Reason: Unclear ("dropped") - Actual outcome: SF-36 General health at After treatment (3 months); Group 1: mean 50.58 (SD 12.84); n=12, Group 2: mean 47.08 (SD 9.4); n=12; SF-36 0-100 Top=High is good outcome; Comments: Baselines, mean (SD): PENS group 48.58 (13.20) Control group 46.83 (10.01) Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Key outcome baselines comparable between experimental and control groups. Differences in baseline for SF-36 Physical role and SF-36 Social functioning. ; Group 1 Number missing: 1, Reason: Unclear ("dropped"); Group 2 Number missing: 1, Reason: Unclear ("dropped") Protocol outcome 2: Pain reduction - Actual outcome: Pain intensity according to VAS at After treatment (3 months); Group 1: mean 2.62 Visual analogue scale (VAS) (SD 2.7); n=12, Group 2: mean 7.87 Visual analogue scale (VAS) (SD 0.88); n=12; Visual analogue scale (VAS) 0-10 Top=High is poor outcome; Comments: Baselines, mean (SD): PENS group 8.08 (1.72) Usual care group 7.95 (1.03) Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Key outcome baselines comparable between experimental and control groups.; Group 1 Number missing: 1, Reason: Unclear ("dropped"); Group 2 Number missing: 1, Reason: Unclear ("dropped")	
Protocol outcomes not reported by the study	Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

Study	Gur 2002[147]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in Turkey; Setting:
Line of therapy	Unclear
Duration of study	Intervention time: 2 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Fibromyalgia patients diagnosed according to the American College of Rheumatology (ACR) criteria for FM.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Fibromyalgia patients fulfilled the American College of Rheumatology (ACR) criteria for FM. These criteria include (a) a history of widespread pain for at least 3 months, i.e., pain in the left or right side of the body, pain above and below the waist, axial skeletal pain (cervical spine or anterior chest or thoracic spine or low back pain) and (b) the presence of at least 11 tender point sites.
Exclusion criteria	Major clinical conditions other than FM were excluded by physical examinations and routine blood cells and differentials, red blood cells, hematocrit and hemoglobin, baseline thyroid-stimulating hormone, and antinuclear autoantibodies. Furthermore, exclusionary criteria for FM patients and normal controls were (a) a recent or past history of psychiatric disorders, e.g., major depressive disorder, alcohol dependence, substance abuse, schizophrenic or paranoid disorder, personality disorders, and somatoform disorders, (b) immunocompromised subjects, (c) subjects with neurological, inflammatory, endocrine, or clinically significant chronic disease such as diabetes mellitus, rheumatoid arthritis, inflammatory bowel disease, and organic brain disorders, (d) abnormal liver function tests such as serum aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and gamma-glutamyl transpeptidase, and (e) pregnant females.
Recruitment/selection of patients	Recruited from Department of Physical Therapy and Rehabilitation, University Hospital of Dicle, Diyarbakyr, Turkey.
Age, gender and ethnicity	Age - Mean (SD): Laser group 30.36 (6.91) ; Placebo group 28.52 (6.28) years. Gender (M:F): 39/11. Ethnicity: Not stated
Further population details	Chronic widespread pain

Extra comments	Disease duration in years, mean (SD): Laser group 4.86 (4.67) Placebo group 4.63 (3.28).
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Electrical Physical Modalities - Laser therapy. Low power laser therapy of approximately 2 J/cm2 was used at each tender point, producing an energy density radiant exposure) at each point. Two physical therapist investigators used standard technique with a Ga-As laser (20 W maximum output per pulse, 904 nm, 200 ns maximum pulse duration, 2.8 kHz pulse frequency, 11.2 mW average power, and 1 cm2 surface (class IIIb Laser Product, Frank Line IR 30, Fysiomed, Belgium). The patients were treated for 3 min at each tender point daily for 2 weeks, except weekends, at the same time in the afternoon in a sitting position and at a temperature of 20C. Duration 2 weeks. Concurrent medication/care: All patients were free of any medications for at least 1 month prior to treatment. Indirectness: No indirectness (n=25) Intervention 2: Placebo/Sham. The same unit as used for the laser intervention was used for the placebo treatment, but no laser beam was emitted. Duration 2 weeks. Concurrent medication/care: All patients were free of any medications for at least 1 month prior to treatment. Indirectness: No indirectness
Funding	Funding not stated

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

Protocol outcome 1: Pain reduction
- Actual outcome: Pain intensity on Likert scale at After treatment (2 weeks); Group 1: mean 1.24 (SD 0.72); n=25, Group 2: mean 2.19 (SD 0.74); n=25; Likert scale for pain (VAS) 0-10 Top=High is poor outcome; Comments: Baselines, mean (SD):
Laser group 3.04 (0.53)
Placebo group 3.19 (0.87)
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing; Group 2 Number missing

Protocol outcomes not reported by the study	Quality of life ; Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

Study	Jales 2015[167]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=20)
Countries and setting	Conducted in Brazil; Setting: Outpatient setting in the Norte Riogranense Institute of Health Research and Teaching (IPENS), Natal/RN.
Line of therapy	Unclear
Duration of study	Intervention time: 10 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosed according to criteria established by the American College of Rheumatology: 1. Widespread Pain Index (WPI) ≥7 and severity symptoms (SS) in a scale of ≥ 5 or WPI between 3 and 6 and SS with score of ≥9; 2. Symptoms are present at similar level for at least three months; 3. Patients have no other disease which could justify the sensation of widespread pain
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Inclusion criteria were patients with FMS, aged between 25 and 65 years, of both genders and living in the city of Natal/RN.
Exclusion criteria	Exclusion criteria were patients with severe cognitive deficits; illiterate; patients with previous and/or family history of seizures; patients with arrhythmias and pacemaker; pregnant and breastfeeding females.
Recruitment/selection of patients	Not stated.
Age, gender and ethnicity	Age - Mean (SD): 46.4 (10.615) years. Gender (M:F): All female. Ethnicity: Not stated
Further population details	Chronic widespread pain
Extra comments	Over 3 months pain by nature of fibromyalgia diagnosis.
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: Electrical Physical Modalities68.5 - Transcranial Direct Current Stimulation (TDCS). For tDCS procedures, two electrodes were positioned on the scalp of patients without causing discomfort and a 1.0mA electric impulse was applied, supplied by an electronic unit with direct current control from Cerebral

	Electronic Stimulator equipment (CES). During procedures, patients remained comfortably lying down in beds, with the anodal electrode positioned on the scalp, on the superior-lateral face of the skull, the region corresponding to the left precentral gyrus (M1 or Brodman's area 4) on its medial third. The cathodic electrode was positioned on the contralateral supraorbital region. A rubber sponge was placed between the scalp and the electrode measuring 3x5cm, previously moistened with 0.9% saline. Direct 1.0mA current was applied for 20 minutes. Duration 10 weeks. Concurrent medication/care: For the duration of the treatment patients were permitted to continue their normal pharmacological and non-pharmacological therapies according to individual situations. Indirectness: No indirectness (n=10) Intervention 2: Placebo/Sham. For the sham tDCS group (control), the same procedures were adopted as for the active tDCS treatment, once a week for 20 minutes for 10 consecutive weeks, but the tDCS device was not turned on. Duration 10 weeks. Concurrent medication/care: For the duration of the treatment patients were permitted to continue their normal pharmacological and non-pharmacological therapies according to individual situations. Indirectness: No indirectness
Funding	Academic or government funding

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

Protocol outcome 1: Quality of life
- Actual outcome: SF-36: Functional capacity at 10 weeks (end of treatment); Group 1: mean 68.5 (SD 11.068); n=10, Group 2: mean 38 (SD 26.895); n=10; SF-36 Quality of life questionnaire 0-100 Top=High is good outcome; Comments: Baselines, mean (SD):
tDCS group 48.00 (16.364)
Sham group 31.00 (23.07)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: SF-36 baselines significantly different in some categories
- Actual outcome: SF-36: Physical aspects at 10 weeks (end of treatment); Group 1: mean 75 (SD 31.18); n=10, Group 2: mean 47.5 (SD 41.583); n=10; SF-36 Quality of life questionnaire 0-100 Top=High is good outcome; Comments: Baselines, mean (SD):
tDCS group 17.5 (23.717)
Sham group 22.5 (36.228)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: SF-36 baselines significantly different in some categories
- Actual outcome: SF-36: Pain at 10 weeks (end of treatment); Group 1: mean 43 (SD 18.288); n=10, Group 2: mean 50 (SD 23.57); n=10; SF-36 Quality of life questionnaire 0-100 Top=High is good outcome; Comments: Baseline, mean (SD):
tDCS group 55 (22.73)
Sham group 62 (13.166)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

- Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: SF-36 baselines significantly different in some categories
- Actual outcome: SF-36: General health status at 10 weeks (end of treatment); Group 1: mean 58 (SD 11.106); n=10, Group 2: mean 63.5 (SD 9.443); n=10; SF-36 Quality of life questionnaire 0-100 Top=High is good outcome; Comments: Baselines, mean (SD):
tDCS group 63.5 (10.554)
Sham group 59 (15.42)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome:. No indirectness ; Baseline details: SF-36 baselines significantly different in some categories
- Actual outcome: SF-36: Vitality at 10 weeks (end of treatment); Group 1: mean 53.5 (SD 9.144); n=10, Group 2: mean 58 (SD 10.055); n=10; SF-36 Quality of life questionnaire 0-100 Top=High is good outcome; Comments: Baselines, mean (SD):
tDCS group 46.5 (10.014)
Sham group 54.5 (6.852)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: SF-36 baselines significantly different in some categories
- Actual outcome: SF-36: General aspects at 10 weeks (end of treatment); Group 1: mean 47.5 (SD 15.366); n=10, Group 2: mean 50 (SD 16.667); n=10; SF-36 Quality of life questionnaire 0-100 Top=High is good outcome; Comments: Baselines, mean (SD):
tDCS group 51.25 (17.129)
Sham group 50 (16.667)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: SF-36 baselines significantly different in some categories
- Actual outcome: SF-36: Emotional aspects at 10 weeks (end of treatment); Group 1: mean 80 (SD 35.633); n=10, Group 2: mean 60 (SD 43.886); n=10; SF-36 Quality of life questionnaire 0-100 Top=High is good outcome; Comments: Baselines, mean (SD):
tDCS group 26.67 (30.633)
Sham group 16.67 (17.566)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: SF-36 baselines significantly different in some categories
- Actual outcome: SF-36: Mental health at 10 weeks (end of treatment); Group 1: mean 58.4 (SD 11.345); n=10, Group 2: mean 54 (SD 11.963); n=10; SF-36 Quality of life questionnaire 0-100 Top=High is good outcome; Comments: Baselines, mean (SD):
tDCS group 53.6 (8.044)
Sham group 51.6 (10.741)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: SF-36 baselines significantly different in some categories

Protocol outcome 2: Pain reduction
- Actual outcome: Pain intensity (VAS) at 10 weeks (end of treatment); Group 1: mean 3.6 (SD 1.838); n=10, Group 2: mean 5.6 (SD 2.503); n=10; Visual analogue scale 0-10 Top=High is poor outcome; Comments: Baselines, mean (SD):
tDCS group 6.05 (2.061)
Sham group 6.70 (2.111)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

- Low, Subgroups - Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

Study	Kabay 2009[176]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=89)
Countries and setting	Conducted in Turkey; Setting: Not specified
Line of therapy	Unclear
Duration of study	Intervention time: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Chronic therapy resistant pelvic pain category IIIB pelvic pain
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosis of category IIIB CP/CPPS as confirmed by detailed history, physical examination, ultrasound, urine flow measurement, residual urine volume measurement, and standard microbiologic cultures. CP/CPPS defined as complaints of pain for at least 6 months in the bladder, groin, genitals, or lower abdomen and or perineal or perianal pain without any obvious abnormalities.
Exclusion criteria	Chronic bacterial prostatitis or category IIIA, aged <18 years, symptoms for less than 6 months, active or recurrent UTIs, STIs, or IC. Other diagnoses such as diabetes, cardiopulmonary disease, neurological disease or other conditions that could explain pain or limit ability to take part in treatment were excluded.
Recruitment/selection of patients	May 2006 to March 2008
Age, gender and ethnicity	Age - Mean (SD): 37.7(7.4) years. Gender (M:F): Not specified. Ethnicity: Not reported
Further population details	Chronic visceral pain
Extra comments	Mean duration of symptoms 4.5(6.1) years
Indirectness of population	No indirectness
Interventions	(n=45) Intervention 1: Electrical Physical Modalities - Percutaneous Electrical Nerve Stimulation (PENS). Percutaneous posterior tibial nerve stimulation. 30 minute sessions, one a week. Needles inserted 5cm from medial malleolus and neutral electrode placed on the same leg, both connected to a stimulator. Electrical stimulation was applied unilaterally with 200-us pulses and a pulse rate of 20Hz, and intensity levels were just below the threshold determining motor contraction. Amplitude was set at maximum tolerable level, usually 1.5

	times the threshold for evoking plantar flexion of toes or toe fanning. Duration 3 months. Concurrent medication/care: Not specified (n=44) Intervention 2: Placebo/Sham. Identical treatment but the electrical stimulation was not applied in the sham group. Duration 3 months. Concurrent medication/care: Not specified
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PERCUTANEOUS ELECTRICAL NERVE STIMULATION (PENS) versus PLACEBO/SHAM Protocol outcome 1: Quality of life - Actual outcome: NIH-CPSI quality of life at 3 months; Group 1: mean 2.1 (SD 0.9); n=45, Group 2: mean 6.7 (SD 2.1); n=44; NIH-CPSI QOL 0-12 Top=High is poor outcome; Comments: Baseline: 6.7(2.2); 6.5(2.8) Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness Protocol outcome 2: Pain reduction - Actual outcome: VAS pain at 3 months; Group 1: mean 4.3 (SD 0.6); n=45, Group 2: mean 7.2 (SD 0.4); n=44; VAS 0-10 Top=High is poor outcome; Comments: Baseline: 7.6(0.8);7.4(0.9) Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

Study	Khedr 2017[185]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=40)
Countries and setting	Conducted in Egypt; Setting: Assiut university hospital
Line of therapy	Unclear
Duration of study	Intervention + follow up: 2 weeks intervention and 8 weeks follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ACR criteria for fibromyalgia
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Met FMS criteria and had score of at least 4 on VAS pain scale
Exclusion criteria	History of autoimmune or chronic inflammatory disease, substance abuse, neuropsychiatric disorders, pregnancy or lactation.
Recruitment/selection of patients	2015-2016, from outpatient clinic
Age, gender and ethnicity	Age - Mean (SD): 32.3(10.9) years. Gender (M:F): 2:34. Ethnicity: Not specified
Further population details	Chronic widespread pain
Extra comments	Duration of symptoms 6.1(2.5) years
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Electrical Physical Modalities - Transcranial Direct Current Stimulation (TDCS). 10 sessions over 2 weeks (5 days of 5 sessions x2). 2mA for 20 mins in each session. Anodal electrode with a current density of 0.08mA placed on left primary motor area, over C3, and reference electrode fixed over contralateral arm. Duration 2 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness (n=20) Intervention 2: Placebo/Sham. Identical treatment but the current applied only for 30s at the beginning and at the end of the session (considered reliable sham stimulation as sensations similar but not enough to induce response). Duration 2 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness

Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS) versus PLACEBO/SHAM Protocol outcome 1: Pain reduction - Actual outcome: VAS at 8 weeks (follow up); Group 1: mean 3.9 (SD 2.1); n=18, Group 2: mean 7.3 (SD 0.9); n=18; VAS 0-10 Top=High is poor outcome; Comments: Baseline: 7.4(1.1); 8(0.8) 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 Protocol outcome 2: Psychological distress - Actual outcome: HAM-A at 8 weeks (follow up); Group 1: mean 11.6 (SD 5.9); n=18, Group 2: mean 17.1 (SD 4.2); n=18; HAM:A Not specified Top=High is poor outcome; Comments: Baseline: 19.3(4.5); 18.7(3.3) 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 - Actual outcome: HAM-D at 8 weeks (follow up); Group 1: mean 19.6 (SD 6.3); n=18, Group 2: mean 17.6 (SD 4); n=18; HAM:D Not specified Top=High is poor outcome; Comments: Baseline: 17.5(4.4); 20.3(3.2) 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	
Protocol outcomes not reported by the study	Quality of life ; Physical function ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

Study	Lee 2012[205]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=22)
Countries and setting	Conducted in South Korea
Line of therapy	Unclear
Duration of study	Intervention + follow up: 10 day intervention and 1 month follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ACR criteria for fibromyalgia
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Chronic, persistent pain for more than 24 months
Exclusion criteria	Evidence of other inflammatory rheumatologic disease or auto-immune disease, or psychiatric disorders, or contraindications for TMS
Recruitment/selection of patients	From division of rheumatology to the neuromodulation outpatient clinic at Adan Medical Center between May 2008 and June 2009
Age, gender and ethnicity	Age - Mean (SD): 47.2(6.2) years. Gender (M:F): All women. Ethnicity: Not specified
Further population details	Chronic widespread pain
Extra comments	Duration of pain 44.7(10.3) years
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: Electrical Physical Modalities - Transcranial Magnetic Stimulation (TMS). Randomised to low frequency stimulation (n=7) or high frequency stimulation (n=8). 1Hz or 10 Hz treatment 5 times per week for 2 weeks of TMS, performed by a physiatrist with a 70-mm air cooled figure of eight shaped coil. Applied to the right side motor cortex, approximate location at the DLPFC. Each patient received either: 1Hz, 110% intensity of resting motor threshold, 800 stimuli of each train (2 trains with 60 secs of intertrain interval and a total of 1600 stimuli per session 10Hz, 80% intensity of resting motor threshold, 2000 stimuli per session. Duration 2 weeks. Concurrent medication/care: Not specified (medications remained unchanged throughout study period). Indirectness: No

	indirectness (n=7) Intervention 2: Placebo/Sham. Identical treatment but coil angle was 90% perpendicular to the skull rather than tangential to it, so the magnetic field could not penetrate the brain, although patients could hear the sound produced. Duration 2 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCRANIAL MAGNETIC STIMULATION (TMS) versus PLACEBO/SHAM Protocol outcome 1: Quality of life - Actual outcome: FIQ at 6 weeks; Group 1: mean 51.8 (SD 13.51); n=10, Group 2: mean 53.7 (SD 27.3); n=5; FIQ 0-100 Top=High is poor outcome; Comments: Baseline: 59.3(23.4); 67.2(11.1);60.4(21.1) Mean of TMS group: weighted mean and SD calculated from LF and HF groups 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: 5; Group 2 Number missing: 2 Protocol outcome 2: Pain reduction - Actual outcome: VAS at 6 weeks; Group 1: mean 60.5 (SD 22.23); n=10, Group 2: mean 72.3 (SD 25.3); n=5; VAS 0-100 Top=High is poor outcome; Comments: Baseline: 72.4(10.7); 70(8.5); 78.1(13.1) Mean of TMS group: weighted mean and SD calculated from LF and HF groups 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: 5; Group 2 Number missing: 2 Protocol outcome 3: Psychological distress - Actual outcome: BDI at 6 weeks; Group 1: mean 17.85 (SD 6.553); n=10, Group 2: mean 18.3 (SD 5.8); n=5; BDI Not reported Top=High is poor outcome; Comments: Baseline: 19.2(4.4); 25.5(6.4); 21.6(5.5) Mean of TMS group calculated from weighted mean and SDs of HF and LF groups 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: 5; Group 2 Number missing: 2 Protocol outcome 4: Discontinuation - Actual outcome: Discontinuation at 6 weeks; Group 1: 5/15, Group 2: 2/7; Comments: 1 in the intervention group discontinued due to a seizure 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: 0, Reason: NA; Group 2 Number missing: 0, Reason: NA	
Protocol outcomes not reported by the study	Physical function ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep

Study	Mhalla 2011[241]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=40)
Countries and setting	Conducted in France; Setting: Not specified
Line of therapy	Unclear
Duration of study	Intervention + follow up: 21 week intervention, follow up at week 25
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ACR criteria for fibromyalgia
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Met ACR criteria, score of at least 4 on BPI, persistent pain for more than 6 months
Exclusion criteria	Inflammatory rheumatic disease, autoimmune disease, or other painful disorders that might confound the assessment of FMS. Any psychiatric condition including major depression or major personality disorders, or history of substance abuse. All women of childbearing age included in this study had negative pregnancy tests at inclusion and were using contraception. Any contraindications for TMS such as seizures or brain trauma. Concomitant medication for pain and sleep allowed provided dose had been stable for at least 1 month before study.
Recruitment/selection of patients	Between 2008 and 2009
Age, gender and ethnicity	Age - Mean (SD): 50.2(10.8) years. Gender (M:F): All female. Ethnicity: Not specified
Further population details	Chronic widespread pain
Extra comments	Pain duration 13.55(12.4) years
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Electrical Physical Modalities - Transcranial Magnetic Stimulation (TMS). 1 session per day for 5 days followed by one weekly session for 3 weeks, 3 fortnightly sessions, and 3 monthly sessions. Patients seated in comfortable chair in relaxed position. MagPROX100 MS device used, using a figure-8 shaped coil oriented at a tangent to the scalp, with the main phase of the induced current in the anterior posterior direction. Resting motor threshold was established in each person, and each session consisted of

	15 series of 10 second pulses with a frequency of 10Hz and an interval of 50 seconds between each train, giving a total of 1500 pulses per session (and stimulation intensity used was 80% of RMT). Duration 21 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness (n=20) Intervention 2: Placebo/Sham. Sham TMS, carried out with identical coil that emitted a sound similar to that emitted by the active coil. Duration 21 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness
Funding	Academic or government funding (Fondation APICIL and the Fondation de France)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCRANIAL MAGNETIC STIMULATION (TMS) versus PLACEBO/SHAM Protocol outcome 1: Quality of life - Actual outcome: FIQ at 25 weeks (follow up); Group 1: mean 56 (SD 17.7); n=15, Group 2: mean 63.3 (SD 15); n=15; FIQ 0-100 Top=High is poor outcome; Comments: Baseline: 66.8(12.5);67.2(14.8) Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness Protocol outcome 2: Psychological distress - Actual outcome: HADS:A at 25 weeks (follow up); Group 1: mean 9.2 (SD 4.9); n=15, Group 2: mean 9.4 (SD 5.7); n=15; HADS:A 0-21 Top=High is good outcome; Comments: Baseline: 11.8(4); 11.4(4.4) Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: HADS:D at 25 weeks (follow up); Group 1: mean 8.6 (SD 4.7); n=15, Group 2: mean 7.4 (SD 4); n=15; HADS:D 0-21 Top=High is poor outcome; Comments: Baseline: 8.4(4.7); 8.7(3.5) Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness Protocol outcome 3: Pain interference - Actual outcome: BPI pain interference at 25 weeks (follow up); Group 1: mean 4.1 (SD 1.7); n=15, Group 2: mean 6 (SD 1.5); n=15; BPI interference Not specified Top=High is poor outcome; Comments: Baseline: 5.8(1.3); 6.1(1.7) Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Pain reduction ; Physical function ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

Study	Murina 2008[250]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=40)
Countries and setting	Conducted in Italy; Setting: Not specified
Line of therapy	Unclear
Duration of study	Intervention time: 10 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of vestibulodynia (positive cotton-swab test with exclusions)
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	All were diagnosed as having vestibulodynia due to the coexistence of the following conditions: a history of at least 6 months of vulval pain upon tampon insertion or attempted intercourse and a positive cotton-swab test, that is, tenderness at palpation of the vestibular area with a cotton tip applicator,8 in the absence of other causes for these findings
Exclusion criteria	pregnancy, cardiac pacemakers, vaginal infections, neurological or neuromuscular disorders and diabetes
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Mean (range): 28(21-44) years. Gender (M:F): All women. Ethnicity: Not specified
Further population details	Chronic visceral pain
Extra comments	Duration of symptoms 15 month (range 7-48 months)
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Electrical Physical Modalities - Transcutaneous Electrical Nerve Stimulation (TENS). TENS group received an electrical stimulation in the form of a symmetrical biphasic wave generated via a calibrated dual channel TENS unit, an YSY-EST device. The stimulation was delivered through a commercially available plastic vaginal probe (PERIPROBE VAG2ST), 20 mm in diameter and 110 mm in length, with two gold metallic transversal rings as electrodes. It was inserted into the vagina for 20 mm. Previous studies involving the use of TENS in women with chronic pain syndromes showed that the optimal analgesic effect was achieved by alternating low- and high-frequency stimulation for 15–30 minutes.12 Based

	on these experiences, frequencies of 10 and 50 Hz at 15-min intervals during each of the active TENS treatment sessions were chosen. The standard protocol for active TENS was 15 minutes of 10-Hz frequency. Duration 10 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness (n=20) Intervention 2: Placebo/Sham. The placebo group received an electrical stimulation considered to be nonactive, that is, two sets of 3-second stimulation (frequency 2 Hz, pulse duration 2 microseconds) followed by a 15-minute pause. Women of both groups underwent 20 treatment sessions on a twice per week basis. Duration 10 weeks. Concurrent medication/care: Not stated. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION (TENS) versus PLACEBO/SHAM

Protocol outcome 1: Pain reduction
- Actual outcome: VAS at 10 weeks; Group 1: mean 2.1 (SD 2.7); n=20, Group 2: mean 5.7 (SD 2.2); n=20; VAS 0-10 Top=High is poor outcome; Comments: Baseline: 6.1(1.9); 6.7(2)
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, Reason: NA; Group 2 Number missing: 0, Reason: NA
- Actual outcome: VAS at 22 weeks (including 10 week intervention); Group 1: mean 2.8 (SD 2.5); n=20, Group 2: mean 5.6 (SD 2.1); n=20; VAS 0-10 Top=High is poor outcome; Comments: Baseline: 6.1(1.9); 6.7(2)
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, Reason: NA; Group 2 Number missing: 0, Reason: NA

Protocol outcome 2: Discontinuation
- Actual outcome: Discontinuation at 10 weeks; Group 1: 0/20, Group 2: 0/20
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, Reason: NA; Group 2 Number missing: 0, Reason: NA

Protocol outcomes not reported by the study	Quality of life ; Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep

Study	Panton 2013[274]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=41)
Countries and setting	Conducted in USA; Setting: Not specified
Line of therapy	Unclear
Duration of study	Intervention time: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ACR criteria for FMS
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	None specified but only women recruited
Exclusion criteria	Participants were excluded if they had uncontrolled hypertension (160/ 100mm Hg or higher), uncontrolled diabetes, active heart disease, known history of cancer, long-term corticosteroid use, pregnant or planning to get pregnant, endocrine disease, anticoagulant therapy, bleeding disorders, history of stroke, a chronic infection, any type of malignancy, if they were taking medications that caused sensitivity to light, if they had a physical examination or radiological findings that would contraindicate the use of light or thermal therapy, and/or currently under the care of a chiropractic physician, acupuncture physician, massage therapist, or other forms of manual therapy.
Recruitment/selection of patients	Participants received $100.00 for participating in the study. Fifty dollars ($50.00) was given after the end of pretesting and another $50.00 was given at the completion of the study.
Age, gender and ethnicity	Age - Mean (SD): 53(11.5) years. Gender (M:F): All women. Ethnicity: Not stated
Further population details	Chronic widespread pain
Extra comments	FMS duration 10.5(7.5) years
Indirectness of population	No indirectness
Interventions	(n=23) Intervention 1: Electrical Physical Modalities - Laser therapy. Delivered by chiropractors. Treatment was designed to be consistent with the laser manufacturer's recommendations and consisted of twice weekly sessions for 4 weeks for a total of 8 sessions. The duration of each session was approximately 15 minutes,

	while actual treatment time was 7 minutes. During the treatment sessions, the participants were either gowned, or wore a sports bra to expose the skin of the cervical, thoracic, and lumbar regions. Participants were positioned face down on a treatment table or a massage chair, depending upon their comfort and preference. Participants wore eye protection with an optical density rating >5.0 at 810nm and 980nm in order to protect their eyes and further obscure which treatment they received. To ensure consistency between the laser and heat and sham and heat group, the treatment targets consisted of seven tender points used as part of the diagnostic criteria to establish a diagnosis of FM (Fig. 1). Treatment was delivered to an area approximately 2.5 inches·3.5 inches or approximately 56.45cm2 to conform to LiteCure's manual ''Clinical Overview and Application of Class IV Therapy Laser'' written by Riegal and Pryor. For the laser group, treatment was rendered utilizing a LCT-1000 (LiteCure LLC, Newark, DE) solid-state GaAlAs laser delivering a continuous-wave, dual-wavelength laser with 20% 810nm, and 80% 980nm at 10W. Each 56.45cm2 treatment point was treated with laser at 10.63J/cm2 and warm air utilizing a grid scanning technique to avoid overheating tissue. Participants were instructed to expect some warmth but that the treatment should not burn and to provide verbal cues if the treatment spots became excessively warm. Each treatment point was treated for exactly 60 seconds for a total of 600J per point, for a total daily treatment dose of 4200J. The dual wavelength was used for two reasons: (1) this is what is commercially available and (2) two wavelengths allow for treatment in patients with different skin colours since different melanin concentrations will absorb light differently. Both wavelengths are in the accepted therapeutic window. The sham treatment consisted of 60 seconds of warm air alone over the seven tender points. A timer was used to ensure that each area was treated for exactly 60 seconds so that the treatment time was identical for both groups. Duration 4 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness (n=18) Intervention 2: Placebo/Sham. Delivered by chiropractors. Because of the thermal affects associated with Class IV laser, and because the laser manufacturer's website specifically mentions the ''soothing warmth'' of laser therapy, a sham and heat therapy treatment was designed to disguise true laser treatment from sham treatment. The device for the treatment was designed to force warm air, provided by a commercially available air warmer through a tube. The air warmer was mounted out of view inside a vented cart upon which the laser was mounted so as to appear as a single unit. The air warmer was mounted to a short section of insulated pipe, which was then attached to a T fitting with a gate valve attached to one side and the warm air supply hose attached to the opposite side. The gate valve was used to control the flow of warm air. The warm air supply hose was then bound together with the laser's fiber-optic cable with zip ties, and wound with white elastic tape to obscure both the tube and the fiber-optic cable. The air supply tube was routed through a hole drilled in the laser handpiece so that warm air could be delivered alone for the sham and heat therapy or in tandem with the laser for the laser and heat therapy. The same device was used for both groups, so the treatment group received both laser and warm air, and the sham group received only warm air. Although neither the skin temperature, nor the warm air output of the treatment device was measured, an effort was made to standardize the heat treatment by utilizing the same medium heat setting for each treatment preceded by a warmup period of approximately 5 minutes to provide a consistent application

	of warm air at approximately the same LASER THERAPY ON FIBROMYALGIA 447 temperature from treatment to treatment. The air flow and temperature were adjusted by way of the gate valve and the air warmer's heat settings in an attempt to mimic the warmth associated with the Class IV laser with sufficient warmth so that participants could not discern whether they received the laser treatment or the sham. Duration 4 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness
Funding	Study funded by industry (Litecure)

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

Protocol outcome 1: Quality of life
- Actual outcome: FIQ at 4 weeks; Group 1: mean 55 (SD 16); n=20, Group 2: mean 55 (SD 12); n=18; FIQ 0-100 Top=High is poor outcome; Comments: Baseline: 62(21); 57(11)
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 3, Reason: Discontinued intervention; Group 2 Number missing: 0, Reason: NA

Protocol outcome 2: Pain reduction
- Actual outcome: FIQ pain at 4 weeks; Group 1: mean 6.2 (SD 2.1); n=20, Group 2: mean 6.1 (SD 1.4); n=18; FIQ pain subscale 0-10 Top=High is poor outcome; Comments: Baseline: 7.1(2.3);5.8(1.3)
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 3, Reason: Discontinued intervention; Group 2 Number missing: 0, Reason: NA

Protocol outcome 3: Discontinuation
- Actual outcome: Discontinuation at 4 weeks; Group 1: 3/23, Group 2: 0/18
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: 0, Reason: NA; Group 2 Number missing: 0, Reason: NA

Protocol outcomes not reported by the study	Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep

Study	Rohlig 2011[289]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=40)
Countries and setting	Conducted in Turkey; Setting: Istanbul University
Line of therapy	Unclear
Duration of study	Intervention time: 3 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of TMD
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Presence of signs and symptoms of TMD of myogenic origin according to the research diagnostic criteria for TMD, orofacial pain lasting for more than 6 months, aged between 18 and 60 years.
Exclusion criteria	Exclusion criteria were disk displacements, arthralgia, arthritis, general inflammatory connective tissue diseases, psychiatric disorders, tumours, heart diseases, pacemakers, pregnancy, symptoms which could be referred to other disorders of the orofacial region, any medication use or treatment for TMD within the last six months, high baseline pain intensity, local skin infections over the TM area.
Recruitment/selection of patients	Selected consecutively among patients requesting orofacial pain treatment over a period of 8 months
Age, gender and ethnicity	Age - Mean (SD): 42.5(2.3) years. Gender (M:F): 16:24. Ethnicity: Not specified
Further population details	1. Chronic orofacial pain
Extra comments	Duration of pain: 10.75(2.9) years
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Electrical Physical Modalities - Laser therapy. Active laser applied every other day for 3 weeks, totalling 10 sessions. A continuous low-intensity semiconductor was used for laser irradiation, generating radiation of 820nm wavelength, with a beam diameter of 6mm and a probe angle of 45 degrees. 8J/cm2 applied to each muscle point for 10 seconds. Duration 3 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness

	(n=20) Intervention 2: Placebo/Sham. Same equipment but the device was not programmed. No further details. Duration 3 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness
Funding	Academic or government funding (Research fund of Istanbul university)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LASER THERAPY versus PLACEBO/SHAM Protocol outcome 1: Pain reduction - Actual outcome: VAS at 3 weeks; Group 1: mean 30.05 (SD 7.14); n=20, Group 2: mean 49.75 (SD 9.54); n=20; VAS 0-100 Top=High is poor outcome; Comments: Baseline: 60.05(10.42); 53.3(8.79) Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: NR, Reason: NR; Group 2 Number missing: NR, Reason: NR	
Protocol outcomes not reported by the study	Quality of life ; Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

Study	Short 2011[314]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=20)
Countries and setting	Conducted in USA; Setting: In the MUSC
Line of therapy	Unclear
Duration of study	Intervention time: 2 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ACR criteria for fibromyalgia
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Subjects could enrol with or without a history of major depressive disorder, but the depression could not be the main reason for their functional impairment or study enrolment. Rather subjects were recruited solely for fibromyalgia pain.
Exclusion criteria	Patients were excluded if they were taking medications known to increase the risk of TMS-induced seizures (e.g., theophylline, Ritalin, high dose thyroid supplementation), if they had medication changes within the 4 weeks of starting the trial or during the trial, or if they had pacemakers, epilepsy, recent head trauma, stroke, bipolar disorder or schizophrenia
Recruitment/selection of patients	2007-2010; Medical University of South Carolina (MUSC) Rheumatology clinics and local newspaper
Age, gender and ethnicity	Age - Mean (SD): 53(13.53) years. Gender (M:F): 4:16. Ethnicity: Not specified
Further population details	Chronic widespread pain
Extra comments	Duration of pain: 11.1(10.36) years
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: Electrical Physical Modalities - Transcranial Magnetic Stimulation (TMS). Both Active and sham groups received the same treatment sessions 5x per week 80 trains × 15 sec = 4000 pulses per

	session, 5 × per week=20,000 pulses per week, × 2weeks = 40,000 pulses. Time - 1200 sec = 20 minutes/session, all days. Resting motor threshold (rMT) was determined using a NeoPulse Neotonus® Model 3600 (with a solid focal coil) TMS machine by starting with 80% of the machine output and 1Hz stimulus frequency. The coil was positioned over the area of the skull roughly corresponding to the motor cortex and then systematically moved and adjusted until each pulse results in isolated movement of the right thumb at rest (Abductor Pollicis Brevis; APB muscle). As the left prefrontal cortex was the cortical target, a mark was made 6 cm anterior to the motor cortex target. During active and sham stimulation, the TMS coil was aligned in a parasaggital orientation, 6 cm from the area that produced right APB muscle movement for rMT testing. The length of treatment and the number of pulses on the head was the same for all subjects; whether they receive active or sham. The same stimulation frequency was used for all active subjects (chosen as a priori stimulation based on studies showing antidepressant and antinociceptive effects): 10 Hertz - Pulse train duration (on time) 5 seconds, Power (intensity)level 120% of resting motor threshold, Inter-train interval (off time) 10seconds (15 second cycle time). Duration 2 weeks. Concurrent medication/care: No further details. Indirectness: No indirectness (n=10) Intervention 2: Placebo/Sham. Both Active and sham groups received the same treatment sessions 5x per week 80 trains × 15 sec = 4000 pulses per session, 5 × per week=20,000 pulses per week, × 2weeks = 40,000 pulses. A specially designed sham TMS coil was used for all sham conditions that produces auditory signals identical to active coils but is shielded so that actual stimulation does not occur, however subjects do experience sensory stimulation that is difficult to distinguish from real TMS. Participants experienced a brief (~250 μs) electrical pulse every time the sham TMS coil clicked. The intensity of the stimulus was adjustable at the electrical generator (1 to 60 mA) and the time that the gate was let open after each TTL trigger was adjustable on the switch-box as well. Duration 2 weeks. Concurrent medication/care: No further details. Indirectness: No indirectness
Funding	Principal author funded by industry (Glaxo-Smith Kline, Jazz Pharmaceuticals, Brainsway, Cephos, and Force Protection)

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

Protocol outcome 1: Quality of life
- Actual outcome: FIQ at 4 weeks; Group 1: mean 38.99 (SD 19.44); n=10, Group 2: mean 47.93 (SD 14.7); n=10; FIQ 0-100 Top=High is poor outcome; Comments: baseline: 58.79(11.93); 54.38(13.96)
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; Baseline details: Number of participants on medications differed (e.g., 20% vs 0% of participants were taking muscle relaxants in the real and sham groups respectively); Group 1 Number missing, Reason: NR; Group 2 Number missing, Reason: NR

Protocol outcome 2: Pain reduction - Actual outcome: VAS at 4 weeks; Group 1: mean 4.41 (SD 1.95); n=10, Group 2: mean 5.37 (SD 2.02); n=10; VAS 0-10 Top=High is poor outcome; Comments: Baseline: 5.6(1.85); 5.34(1.82) 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; Baseline details: Number of participants on medications differed (e.g., 20% vs 0% of participants were taking muscle relaxants in the real and sham groups respectively); Group 1 Number missing, Reason: NR; Group 2 Number missing, Reason: NR Protocol outcome 3: Physical function - Actual outcome: Brief pain inventory functional impairment at 4 weeks; Group 1: mean 3.6 (SD 2.18); n=10, Group 2: mean 3.79 (SD 2.69); n=10; BPI subscale 0-10 Top=High is poor outcome; Comments: Baseline: 5.57(2.58); 5.44(2.25) 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; Baseline details: Number of participants on medications differed (e.g., 20% vs 0% of participants were taking muscle relaxants in the real and sham groups respectively); Group 1 Number missing, Reason: NR; Group 2 Number missing, Reason: NR Protocol outcome 4: Psychological distress - Actual outcome: Hamilton depression rating scale at 4 weeks; Group 1: mean 14.1 (SD 9.42); n=10, Group 2: mean 16.4 (SD 8.18); n=10; HDRS 0-52 Top=High is poor outcome; Comments: Baseline:21.8(7.79); 17.6(7.31) 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; Baseline details: Number of participants on medications differed (e.g., 20% vs 0% of participants were taking muscle relaxants in the real and sham groups respectively); Group 1 Number missing, Reason: NR; Group 2 Number missing, Reason: NR	
Protocol outcomes not reported by the study	Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

Study	Spanemberg 2015[325]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=58)
Countries and setting	Conducted in Spain; Setting: Not specified
Line of therapy	Unclear
Duration of study	Intervention time: 3 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of burning mouth syndrome
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Above 40 years old, burning or pain in the oral mucosa for at least 6 months with clinically normal mucosa.
Exclusion criteria	Participants who were taking antidepressants, anxiolytic or anticonvulsant drugs or those who had undergone chemotherapy or radiotherapy were excluded. Patients who showed hyposalivation, alterations in blood count, glucose serum levels, iron, folic acid, vitamin b12 were also excluded.
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Mean (SD): 61.9(8.76) years. Gender (M:F): 8:51. Ethnicity: Not specified
Further population details	1. Chronic orofacial pain: Chronic orofacial pain
Extra comments	Duration of pain not specified (minimum duration 6 months)
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Electrical Physical Modalities - Laser therapy. Infrared laser therapy 3 times a week. GaA1As, 830nm wavelength, 100mW output, continuous emissions, 3.57W/cm2, 5J energy per point, 176J/cm2 radiant exposure, application time 50s per point. Total 9 sessions. Duration 3 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=19) Intervention 2: Electrical Physical Modalities - Laser therapy. Red laser therapy: InGaAlP, 685nm wavelength, 35mW output power, continuous emissions, 1.25W/cm2, 2J energy per point, 72 J/cm2 radiant exposure, application time 58s per point. Total 9 sessions (3 per week). Duration 3 weeks. Concurrent

	medication/care: Not specified. Indirectness: No indirectness (n=19) Intervention 3: Placebo/Sham. 9 sessions, similar to both laser interventions but the tool received a plastic tip with rubber interior that blocked radiation emissions, checked by means of a power meter prior to the applications. Duration 3 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness
Funding	Study funded by industry (Coorednacao de Aperfeicoamento de Pesal de Nivel Superior (CAPES) - Brazil)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LASER THERAPY (INFRARED) versus PLACEBO/SHAM Protocol outcome 1: Quality of life - Actual outcome: Oral health impact profile at 3 weeks; Group 1: mean 6.89 (SD 4.05); n=20, Group 1: mean 13.39 (SD 3.62); n=19 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: Pain reduction - Actual outcome: VAS at 8 weeks follow up (including 3 week intervention); Group 1: mean 25.9 (SD 19.48); n=20, Group 2: mean 62.84 (SD 26.3); n=19; VAS 0-100 Top=High is poor outcome; Comments: Baseline: 85.26(14.25); 78.9(15.25) 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 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LASER THERAPY (RED) versus PLACEBO/SHAM Protocol outcome 1: Quality of life - Actual outcome: Oral health impact profile at 3 weeks; Group 1: mean 9.77 (SD 4.92); n=19, Group 2: mean 13.39 (SD 3.62); n=19; OHIP Not specified Top=High is poor outcome; Comments: Baseline: 14.46(7.21); 17.8(5.37) 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: Pain reduction - Actual outcome: VAS at 8 weeks follow up (including 3 week intervention); Group 1: mean 41.11 (SD 27.14); n=19, Group 2: mean 62.84 (SD 26.3); n=19; VAS 0-100 Top=High is poor outcome; Comments: Baseline: 85.26(14.25);80.68(18.63) 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	Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

Study	Sugaya 2016[329]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=30)
Countries and setting	Conducted in Brazil; Setting: Not specified
Line of therapy	Unclear
Duration of study	Intervention time: 2 week intervention plus 90 days follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Met the diagnostic criteria for burning mouth syndrome
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Other diagnoses ruled out (diabetes, anemia, hypovitaminosis).
Exclusion criteria	Clinical alterations in the oral mucosa potentially associated with the burning symptoms, hyposalivation, diabetes, B hypovitaminosis, and anemia. History of malignant of benign head and neck neoplasia, pregnancy, breast feeding
Recruitment/selection of patients	Stomatology Clinic of the Sao Paulo University School of Dentistry
Age, gender and ethnicity	Age - Mean (range): 59.7(29-83) years. Gender (M:F): 2:21. Ethnicity: Not specified
Further population details	1. Chronic orofacial pain: Chronic orofacial pain
Extra comments	Mean duration of symptoms 31.7 months (range 6 to 192)
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: Electrical Physical Modalities - Laser therapy. 4 sessions of irradiation across 2 weeks, with a 3 day interval between each session. Laser irradiation delivered in scanning mode with laser point in contact with the mucosa. The energy released was 6J/cm2, and irradiation was applied on the entire area affected by the burning sensation. Irradiation time was determined by the extension of the affected area, according to a standardised formula. Duration 2 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness

	(n=15) Intervention 2: Placebo/Sham. Identical method but no laser energy was delivered. The machine still beeped at regular intervals so it appeared active. Duration 2 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness
Funding	Academic or government funding (State of Sao Paulo research foundation)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LASER THERAPY versus PLACEBO/SHAM Protocol outcome 1: Pain reduction - Actual outcome: VAS (calculated from individual patient data) at 3 months; Group 1: mean 2 (SD 1.89); n=13, Group 2: mean 2.2 (SD 1.94); n=10; VAS 0-10 Top=High is poor outcome; Comments: Baseline not reported Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2; Group 2 Number missing: 5 - Actual outcome: VAS (calculated from individual patient data) at 16 weeks; Group 1: mean 2.08 (SD 2.25); n=13, Group 2: mean 1.8 (SD 1.89); n=10; VAS 0-10 Top=High is poor outcome; Comments: Baseline values not reported Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2; Group 2 Number missing: 5	
Protocol outcomes not reported by the study	Quality of life ; Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

Study	Tekin 2014[339]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=52)
Countries and setting	Conducted in Turkey; Setting: Not specified
Line of therapy	Unclear
Duration of study	Intervention time: 10 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ACR FMS criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Right handed, 18-65 years old, no analgesic use for at least 1 month, suffered persistent pain for longer than 6 months
Exclusion criteria	Causes of pain such as inflammatory or rheumatologic diseases, other pain related diseases, psychiatric disorders other than depression, drug abuse or dependency, or patients contraindicated to electrical therapy (e.g. epilepsy or head trauma).
Recruitment/selection of patients	2012-2013, patients who were evaluated at the Sisli Etfal education and research hospital physical medicine and rehab outpatient unit
Age, gender and ethnicity	Age - Mean (SD): 44.4(8.1) years. Gender (M:F): 4:47. Ethnicity: Not specified
Further population details	Chronic widespread pain
Extra comments	Duration of pain 12.1(6.47) years
Indirectness of population	No indirectness
Interventions	(n=27) Intervention 1: Electrical Physical Modalities - Transcranial Magnetic Stimulation (TMS). Repetitive TMS conducted with Magstim biphasic stimulation device with 8 shaped coil of 70mm. Conducted by a psychiatry physician. Resting motor threshold values determined for each patient using the minimum motor threshold method. Sessions conducted as 30 sequential series, for 5s, frequency 10Hz, application intensity 100%, interval between the series was 12s (total of 1500 stimuli per day given to each patient). Duration 10 days. Concurrent medication/care: Not specified. Indirectness: No indirectness

	(n=25) Intervention 2: Placebo/Sham. Identical treatment but a placebo coil system was used which produced similar sounds to the real application but without magnetic stimulation. Duration 10 days. Concurrent medication/care: Not specified. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCRANIAL MAGNETIC STIMULATION (TMS) versus PLACEBO/SHAM Protocol outcome 1: Quality of life - Actual outcome: WHOQOL-BREF physical domain at 10 days; Group 1: mean 14.26 (SD 2.52); n=27, Group 2: mean 11.33 (SD 2.84); n=24; WHOQOL-BREF 4-20 Top=High is good outcome; Comments: baseline: 11.07(2.54); 10.83(2.79) 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: 0, Reason: NA; Group 2 Number missing: 1, Reason: NR - Actual outcome: WHOQOL-BREF psychological domain at 10 days; Group 1: mean 13.89 (SD 2.47); n=27, Group 2: mean 12.71 (SD 2.49); n=24; WHOQOL-BREF 4-20 Top=High is good outcome; Comments: Baseline: 12.15(2.57); 12.29(2.85) 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: 0, Reason: NA; Group 2 Number missing: 1, Reason: NR Protocol outcome 2: Pain reduction - Actual outcome: VAS at 10 days; Group 1: mean 37.96 (SD 9.83); n=27, Group 2: mean 62.08 (SD 16.68); n=24; VAS 0-100 Top=High is poor outcome; Comments: Baseline: 79.63(12.24); 81.25(12.9) 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: 0, Reason: NA; Group 2 Number missing: 1, Reason: NR Protocol outcome 3: Psychological distress - Actual outcome: MADRS at 10 days; Group 1: mean 10.14 (SD 3.96); n=27, Group 2: mean 10.24 (SD 6); n=24; MADRS Not specified Top=High is poor outcome; Comments: Baseline: 12.89(4.53); 12.25(6.44) 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: 0, Reason: NA; Group 2 Number missing: 1, Reason: NR Protocol outcome 4: Discontinuation - Actual outcome: Discontinuation from treatment at 10 days; Group 1: 0/27, Group 2: 1/25 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: 0, Reason: NA; Group 2 Number missing: 1, Reason: NR	
Protocol outcomes not reported by the study	Physical function ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep

Study	Umezaki 2016[345]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=26)
Countries and setting	Conducted in USA; Setting: MUSC
Line of therapy	Unclear
Duration of study	Intervention + follow up: 10 day treatment and 8 weeks follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of burning mouth syndrome
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosis of BMS confirmed by (1) daily and deep bilateral burning sensation of the oral mucosa, burning sensation for at least 4-56 months, constant intensity or increasing intensity during the day, no worsening but possible improvement on eating or drinking, no interference with sleep and normal appearing oral mucosa
Exclusion criteria	Excluded one evidence of inflammation or autoimmune disease, current psychiatric conditions or drug abuse, or other contradictions for TMS, or starting new medication or changing medication within 4 weeks of starting the trial
Recruitment/selection of patients	Recruited through local newspaper adverts, from the oral pathology division in the MUSC dental clinic and through MUSC broadcast email
Age, gender and ethnicity	Age - Mean (SD): 63.85(9.56) years. Gender (M:F): 92.31% female. Ethnicity: Not specified
Further population details	1. Chronic orofacial pain
Extra comments	Duration of illness 63.42(65.51) years
Indirectness of population	No indirectness
Interventions	(n=14) Intervention 1: Electrical Physical Modalities - Transcranial Magnetic Stimulation (TMS). Device: MagVenture MagPro x100 stimulator with figure 8 coil. Resting motor threshold determined each for each individual. Machine set at 50% maximum output and TMS coil positioned around primary motor cortex, and moved until the area that best produced contraction of abductor pollicis brevis was identified. 10 sessions of 10Hz pulse train duration 5s, power intensity levels 110% of RMT, intertrain interval 10s for 15 minutes (total

	of 30,000 pulses). Duration 1 week. Concurrent medication/care: Not specified. Indirectness: No indirectness (n=12) Intervention 2: Placebo/Sham. Identical treatment but the coil was shielded so that actual stimulation did not occur. Duration 1 week. Concurrent medication/care: Not specified. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCRANIAL MAGNETIC STIMULATION (TMS) versus PLACEBO/SHAM Protocol outcome 1: Pain reduction - Actual outcome: Pain (McGill pain questionnaire) at 8 weeks (follow up); Group 1: mean 1.33 (SD 0.78); n=12, Group 2: mean 2.88 (SD 1.36); n=8; SFMPQ Not specified Top=High is poor outcome; Comments: Baseline: 2.54(0.84); 3.63(1.51) Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: Lost to follow up; Group 2 Number missing: 4, Reason: Lost to follow up Protocol outcome 3: Discontinuation - Actual outcome: Discontinued intervention at 1 week; Group 1: 0/14, Group 2: 0/12 Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: Lost to follow up; Group 2 Number missing: 4, Reason: Lost to follow up	
Protocol outcomes not reported by the study	Quality of life ; Physical function ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep

Study	Valenzuela 2017[346]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=44)
Countries and setting	Conducted in Spain; Setting: Not specified
Line of therapy	Unclear
Duration of study	Intervention time: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Burning mouth syndrome diagnosis according to international classification of headaches
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	BMS diagnosis, continuous symptoms of oral burning or pain on a daily or almost daily basis during all or part of the day for more than 6 months and absence of local or systemic factors that could produce the same symptoms
Exclusion criteria	History of head and neck malignancy radiation therapy to the head and neck area, poorly managed conditions such as diabetes, thyroid disease, Sjorgrens syndrome, rheumatological diseases, anemia, analgesics or NSAID use, pregnancy.
Recruitment/selection of patients	Consecutive patients diagnosed with idiopathic burning mouth syndrome attending the department of oral medicine (FoM and Dentistry, UoM, Spain).
Age, gender and ethnicity	Age - Mean (SD): 65.5 (10.6) years. Gender (M:F): 3:41. Ethnicity: Not specified
Further population details	1. Chronic orofacial pain
Extra comments	Duration of pain not specified
Indirectness of population	No indirectness
Interventions	(n=16) Intervention 1: Electrical Physical Modalities - Laser therapy. Low level laser. 815nm wavelength, 1W output power, 4 seconds, 4J, fluence rate 133.3Jcm-2. Applied intra-orally and continuously, perpendicularly in contact with the mucosa in areas where patient reported symptoms. Spot sizes were 0.03cm3 and ten points over each area presenting symptoms were irradiated. Duration 4 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness

	(n=16) Intervention 2: Electrical Physical Modalities - Laser therapy. Low level laser. 815nm wavelength, 1W output power, 6 seconds, 6J, fluence rate 200Jcm-2. Applied intra-orally and continuously, perpendicularly in contact with the mucosa in areas where patient reported symptoms. Spot sizes were 0.03cm3 and ten points over each area presenting symptoms were irradiated. Duration 4 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness (n=12) Intervention 3: Placebo/Sham. Sham: same procedure but laser turned off. Duration 4 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LASER THERAPY (LOW INTENSITY) versus PLACEBO/SHAM

Protocol outcome 1: Quality of life
- Actual outcome: Oral health impact profile at 4 weeks; Group 1: mean 28.5 (SD 3.1); n=16, Group 2: mean 29.25 (SD 6.1); n=12; OHIP 0-70 Top=High is poor outcome; Comments: Baseline: 29.88(3.6); 29.33(5.9)
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: NR; Group 2 Number missing: NR

Protocol outcome 2: Pain reduction
- Actual outcome: VAS at 4 weeks; Group 1: mean 6.38 (SD 1.6); n=16, Group 2: mean 7.65 (SD 1.2); n=12; VAS 0-10 Top=High is poor outcome; Comments: Baseline: 7.56(1.5); 7.83(1.3)
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: NR; Group 2 Number missing: NR

Protocol outcome 3: Psychological distress
- Actual outcome: HADS:A at 4 weeks; Group 1: mean 10.44 (SD 3.9); n=16, Group 2: mean 10.33 (SD 3.5); n=12; HADS:A 0-21 Top=High is poor outcome; Comments: Baseline: 10.44(3.9); 10.25(3.5)
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:: NR; Group 2 Number missing: NR
- Actual outcome: HADS:D at 4 weeks; Group 1: mean 7.19 (SD 4.9); n=16, Group 2: mean 7.25 (SD 4.5); n=12; HADS:D 0-21 Top=High is poor outcome; Comments: Baseline: 7.19(4.9); 7.25(4.5)
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: NR; Group 2 Number missing: NR

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LASER THERAPY (HIGH INTENSITY) versus PLACEBO/SHAM

Protocol outcome 1: Quality of life - Actual outcome: Oral health impact profile at 4 weeks; Group 1: mean 28.25 (SD 6.1); n=16, Group 2: mean 29.25 (SD 6.3); n=12; OHIP 0-70 Top=High is poor outcome; Comments: Baseline: 29.57(5.9); 29.33(5.9) Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: NR; Group 2 Number missing: NR Protocol outcome 2: Pain reduction - Actual outcome: VAS at 4 weeks; Group 1: mean 7.06 (SD 1.8); n=16, Group 2: mean 7.65 (SD 1.2); n=12; VAS 0-10 Top=High is poor outcome; Comments: Baseline: 8.38(1.3); 7.83(1.3) Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: NR; Group 2 Number missing: NR Protocol outcome 3: Psychological distress - Actual outcome: HADS:A at 4 weeks; Group 1: mean 11.88 (SD 3.2); n=16, Group 2: mean 10.33 (SD 3.5); n=12; HADS:A 0-21 Top=High is poor outcome; Comments: Baseline: 11.75(3.4); 10.25(3.5) Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: NR; Group 2 Number missing: NR - Actual outcome: HADS:D at 4 weeks; Group 1: mean 9.88 (SD 3.3); n=16, Group 2: mean 7.25 (SD 4.5); n=12; HADS:D 0-21 Top=High is poor outcome; Comments: Baseline: 10(3.3); 7.25(4.5) 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 at baseline in outcome: 10(3.3); 7.25(4.5); Group 1 Number missing:: NR; Group 2 Number missing: NR	
Protocol outcomes not reported by the study	Physical function ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

Study	Venancio 2005[354]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=30)
Countries and setting	Conducted in Brazil; Setting: Not specified
Line of therapy	Unclear
Duration of study	Intervention + follow up: 3 weeks (with 8 week follow up)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: TMD diagnosis according to criteria of the American Academy of Orofacial pain
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Pain restricted to the joint area, associated with the absence of any muscle tenderness during palpation.
Exclusion criteria	Psychiatric disorders, heart diseases, epilepsy, pregnancy, RA, degenerative joint disease, tumours, people with pacemakers
Recruitment/selection of patients	Consecutive patients that presented for diagnosis and treatment of TMD in the OTDC clinic at a dentistry school.
Age, gender and ethnicity	Age - Mean (range): 36.25(13-63) years. Gender (M:F): 5:25. Ethnicity: Not specified
Further population details	1. Chronic orofacial pain
Extra comments	Mean duration of pain 44.8 months (range 6-120 months)
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: Electrical Physical Modalities - Laser therapy. Twice a week for 3 weeks. Using Ga0Al-As laser at 780nm wavelength. Output of 30mW, 10s duration, at 6.3Jcm-2 at 3 points in each TMJ. Duration 3 weeks. Concurrent medication/care: Not reported (other than advice about resting joints, following a soft diet and conscious relaxation of masticatory muscles). Indirectness: No indirectness (n=15) Intervention 2: Placebo/Sham. Identical treatment but the laser device was not turned on. Duration 3 weeks. Concurrent medication/care: Not reported (other than advice about resting joints, following a soft diet

	and conscious relaxation of masticatory muscles). Indirectness: No indirectness
Funding	Academic or government funding (FAPESP Sao Paulo Research Support Foundation)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LASER THERAPY versus PLACEBO/SHAM Protocol outcome 1: Pain reduction - Actual outcome: VAS at 8 weeks; Group 1: mean 1.6 (SD 2.03); n=15, Group 2: mean 3.67 (SD 2.85); n=15; VAS 0-10 Top=High is poor outcome Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life ; Physical function ; Psychological distress ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

Study	Yagci 2014[375]
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	(n=28)
Countries and setting	Conducted in Turkey; Setting: Not specified
Line of therapy	Unclear
Duration of study	2 week intervention and 3 months follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ACR criteria for fibromyalgia
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 18-60 years, no improvement in symptoms regardless of using medical treatment for at least 3 months.
Exclusion criteria	Other diagnoses such as inflammatory rheumatic disease, current primary psychiatric disease, previous surgical treatment to the cranial area, pregnancy, or history of substance abuse
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Mean (SD): 44.9(8.6) years. Gender (M:F): All female. Ethnicity: Not specified
Further population details	Chronic widespread pain
Extra comments	Mean duration of symptoms 53.5 (29.8) months
Indirectness of population	No indirectness
Interventions	(n=14) Intervention 1: Electrical Physical Modalities - Transcranial Magnetic Stimulation (TMS). 2 week interventions, with 10 sessions of low-frequency rTMS applied from Monday to Friday of each week. The stimulation area was the left primary motor cortex. Magnetic stimulation applied using a MagBenture machine, using a parabolic coil that was oriented at a tangent to the scalp. The resting motor threshold was determined before each session using single pulse stimulation over the left primary motor cortex, which was defined as the minimal intensity required to evoke MEPs of 50mV peak-to-peak amplitude in 5 out of 10 consecutive trials. The main stimulation parameters were 90% of motor threshold for 60 seconds at 1Hz and 45 second intervals between each trains. 1200 pulses were therefore administered in each session. Duration 2 weeks. Concurrent medication/care: Medications remained stable throughout the study. Indirectness: No indirectness

	(n=14) Intervention 2: Placebo/Sham. Sham stimulation carried out with the same parabolic coil, which was placed at 90 degree angles to the motor cortex area. No further details. Duration 2 weeks. Concurrent medication/care: Medications remained stable throughout. Indirectness: No indirectness
Funding	Not reported
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCRANIAL MAGNETIC STIMULATION (TMS) versus PLACEBO/SHAM Protocol outcome 1: Quality of life - Actual outcome: FIQ at 3 months; Group 1: mean 36.95 (SD 24.27); n=13, Group 2: mean 48.13 (SD 16.79); n=12; VAS 0-10 Top=High is poor outcome; Comments: Baseline: 66.09(15.13); 65.1(12.92) 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 ; Baseline details: Beck depression inventory baseline difference; Group 1 Number missing: 1, Reason: NR; Group 2 Number missing: 2, Reason: NR Protocol outcome 2: Pain reduction - Actual outcome: VAS at 3 months; Group 1: mean 4.75 (SD 2.76); n=13, Group 2: mean 5.3 (SD 2.49); n=12; VAS 0-10 Top=High is poor outcome; Comments: Baseline: 7.75(1.54); 7.61(2.14) 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 ; Baseline details: Beck depression inventory baseline difference; Group 1 Number missing: 1, Reason: NR; Group 2 Number missing: 2, Reason: NR Protocol outcome 3: Psychological distress - Actual outcome: BDI at 3 months; Group 1: mean 16.75 (SD 10.6); n=13, Group 2: mean 14.15 (SD 8); n=12; Beck depression inventory 0-61 Top=High is poor outcome; Comments: Baseline: 19.58(9.33);18.53(9.7) 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 ; Baseline details: Beck depression inventory baseline difference; Group 1 Number missing: 1, Reason: NR; Group 2 Number missing: 2, Reason: NR	
Protocol outcomes not reported by the study	Physical function ; Pain interference ; Pain self-efficacy ; Use of healthcare services ; Sleep ; Discontinuation

Appendix E: Forest plots

E.1 Laser therapy versus sham laser therapy

Figure 2: Quality of life at ≤3 months (Oral health impact profile, FIQ, high is poor outcome, final values)

	Laser			Sham laser				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Arbabi-Kalati 2015	12.8	11.4	10	28.6	11.5	10	11.1%	-1.32 [-2.31, -0.33]
Armagan 2006	58.5	10.33	16	63.63	9.59	16	15.8%	-0.50 [-1.21, 0.20]
Bardellini 2019	7.09	2.59	43	10.64	4.13	42	21.2%	-1.02 [-1.48, -0.57]
Panton 2013	55	16	20	55	12	18	17.2%	0.00 [-0.64, 0.64]
Spanemberg 2015	8.293	4.72	39	13.39	3.62	19	18.2%	-1.14 [-1.73, -0.55]
Valenzuela 2017	28.38	4.84	31	29.25	6.1	12	16.5%	-0.16 [-0.83, 0.50]
Total (95% CI)			**159**			**117**	**100.0%**	**-0.68 [-1.10, -0.25]**

Heterogeneity: Tau² = 0.17; Chi² = 13.07, df = 5 (P = 0.02); I² = 62%
Test for overall effect: Z = 3.12 (P = 0.002)

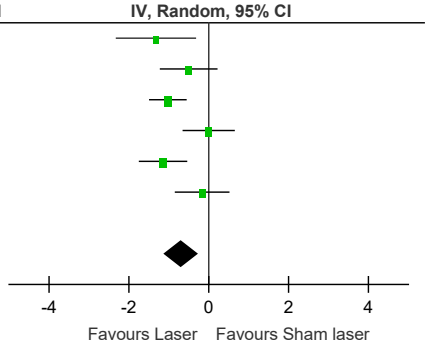


Figure 3: Quality of life at ≤3 months (SF-36 physical component summary score, 0-100, high is good outcome, change scores)

	Laser			Sham laser				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Chow 2004	4	8.22	10	1.22	6.32	10	21.8%	2.78 [-3.65, 9.21]
Chow 2006	3.2	10.78	45	1.3	4.28	45	78.2%	1.90 [-1.49, 5.29]
Total (95% CI)			**55**			**55**	**100.0%**	**2.09 [-0.91, 5.09]**

Heterogeneity: Chi² = 0.06, df = 1 (P = 0.81); I² = 0%
Test for overall effect: Z = 1.37 (P = 0.17)

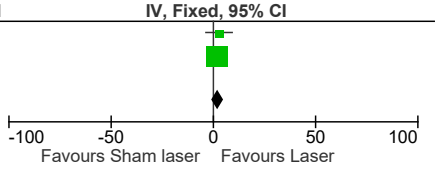


Figure 4: Quality of life at ≤3 months (SF-36 mental component summary score, 0-100, high is good outcome, change scores)

	Laser			Sham laser				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Chow 2004	1.71	3.79	10	0	6.01	10	48.0%	1.71 [-2.69, 6.11]
Chow 2006	2.4	8.2	45	5.4	10.9841	45	52.0%	-3.00 [-7.00, 1.00]
Total (95% CI)			**55**			**55**	**100.0%**	**-0.74 [-5.35, 3.87]**

Heterogeneity: Tau² = 6.48; Chi² = 2.41, df = 1 (P = 0.12); I² = 58%
Test for overall effect: Z = 0.31 (P = 0.75)

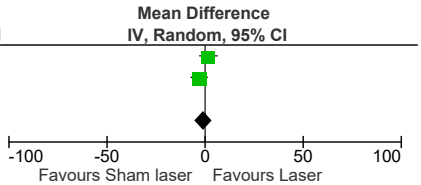


Figure 5: Quality of life at >3 months (FIQ, 0-100, high is poor outcome, final values)

	Laser			Sham laser				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Armagan 2006	62.06	8.99	16	66.94	8.44	16	28.4%	-0.55 [-1.25, 0.16]
Bardellini 2019	7.43	3.78	43	10.43	2.99	42	71.6%	-0.87 [-1.32, -0.43]
Total (95% CI)			**59**			**58**	**100.0%**	**-0.78 [-1.16, -0.40]**

Heterogeneity: Chi² = 0.58, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 4.05 (P < 0.0001)

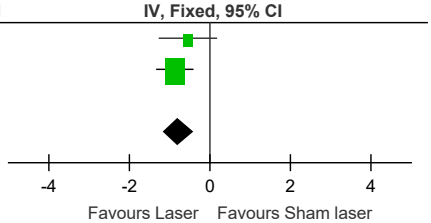
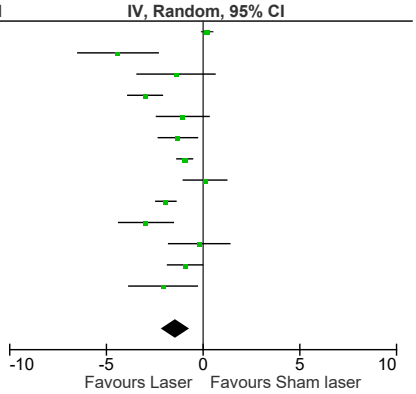


Figure 6: Pain reduction at ≤3 months (VAS, NRS, FIQ pain scale, high is poor outcome, 0-10, final values and change scores)

Study or Subgroup	Laser Mean	Laser SD	Laser Total	Sham laser Mean	Sham laser SD	Sham laser Total	Weight	Mean Difference IV, Random, 95% CI
Altan 2005	4.13	0.58	23	3.92	0.42	25	9.8%	0.21 [-0.08, 0.50]
Arbabi-Kalati 2015	3.6	3	10	8	1.5	10	5.3%	-4.40 [-6.48, -2.32]
Chow 2004	-2.1	2.84	10	-0.7	1.58	10	5.4%	-1.40 [-3.41, 0.61]
Chow 2006	-2.7	1.9971	45	0.3	2.33	45	8.6%	-3.00 [-3.90, -2.10]
da Cunha 2008	3.62	2.45	20	4.67	1.9	20	7.2%	-1.05 [-2.41, 0.31]
Del vecchio 2019	-3.517	2.2139	29	-2.214	1.6635	28	8.2%	-1.30 [-2.32, -0.29]
Gur 2002	1.24	0.72	25	2.19	0.74	25	9.7%	-0.95 [-1.35, -0.55]
Panton 2013	6.2	2.1	20	6.1	1.4	18	7.9%	0.10 [-1.02, 1.22]
Rohlig 2011	3.05	0.714	20	4.975	0.954	20	9.5%	-1.92 [-2.45, -1.40]
Spanemberg 2015	3.33	2.47	39	6.284	2.63	19	7.1%	-2.95 [-4.37, -1.54]
Sugaya 2016	2	1.89	13	2.2	1.94	10	6.6%	-0.20 [-1.78, 1.38]
Valenzuela 2017	6.72	1.74	32	7.65	1.2	12	8.5%	-0.93 [-1.84, -0.02]
Venancio 2005	1.6	2.03	15	3.67	2.85	15	6.1%	-2.07 [-3.84, -0.30]
Total (95% CI)			**301**			**257**	**100.0%**	**-1.42 [-2.12, -0.73]**

Heterogeneity: Tau² = 1.27; Chi² = 114.87, df = 12 (P < 0.00001); I² = 90%
Test for overall effect: Z = 4.00 (P < 0.0001)

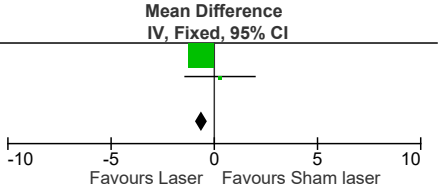


1

Figure 7: Pain reduction at >3 months (VAS, high is poor outcome, 0-10, final values)

Study or Subgroup	Laser Mean	Laser SD	Laser Total	Sham laser Mean	Sham laser SD	Sham laser Total	Weight	Mean Difference IV, Fixed, 95% CI
Altan 2005	3.17	0.58	23	3.8	0.51	25	96.8%	-0.63 [-0.94, -0.32]
Sugaya 2016	2.08	2.25	13	1.8	1.89	10	3.2%	0.28 [-1.41, 1.97]
Total (95% CI)			**36**			**35**	**100.0%**	**-0.60 [-0.91, -0.30]**

Heterogeneity: Chi² = 1.07, df = 1 (P = 0.30); I² = 7%
Test for overall effect: Z = 3.86 (P = 0.0001)

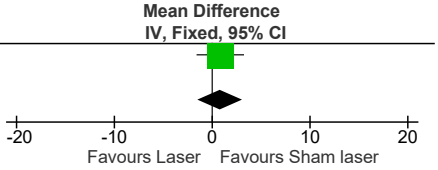


2

Figure 8: Psychological distress at ≤3 months (Hospital anxiety and depression rating scale, anxiety subscale, 0-21, high is poor outcome, final values)

Study or Subgroup	Laser Mean	Laser SD	Laser Total	Sham laser Mean	Sham laser SD	Sham laser Total	Weight	Mean Difference IV, Fixed, 95% CI
Valenzuela 2017	11.16	3.639	32	10.33	3.5	12	100.0%	0.83 [-1.52, 3.18]
Total (95% CI)			**32**			**12**	**100.0%**	**0.83 [-1.52, 3.18]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)

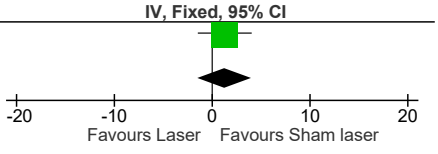


3

Figure 9: Psychological distress at ≤3 months (Hospital anxiety and depression rating scale, depression subscale, 0-21, high is poor outcome, final values)

Study or Subgroup	Laser Mean	Laser SD	Laser Total	Sham laser Mean	Sham laser SD	Sham laser Total	Weight	Mean Difference IV, Fixed, 95% CI
Valenzuela 2017	8.535	4.389	32	7.25	4.5	16	100.0%	1.29 [-1.39, 3.96]
Total (95% CI)			**32**			**16**	**100.0%**	**1.29 [-1.39, 3.96]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.94 (P = 0.35)

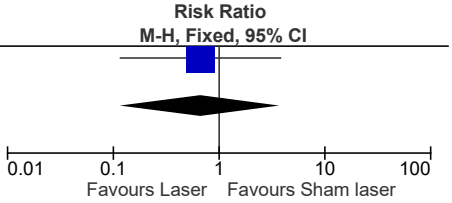


4

Figure 10: Discontinuation at ≤3 months

Study or Subgroup	Laser Events	Laser Total	Sham laser Events	Sham laser Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chow 2006	2	45	3	45	100.0%	0.67 [0.12, 3.80]
Total (95% CI)		**45**		**45**	**100.0%**	**0.67 [0.12, 3.80]**
Total events	2		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.46 (P = 0.65)



E.2 TMS versus sham TMS

Figure 11: Quality of life at ≤3 months (SF-36 physical summary score, 0-100, high is good outcome, change scores)

Study or Subgroup	TMS Mean	TMS SD	TMS Total	Sham TMS Mean	Sham TMS SD	Sham TMS Total	Weight	Mean Difference IV, Fixed, 95% CI
Boyer 2014	1.4	9	16	0.4	4.8	13	100.0%	1.00 [-4.12, 6.12]
Total (95% CI)			**16**			**13**	**100.0%**	**1.00 [-4.12, 6.12]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.38 (P = 0.70)

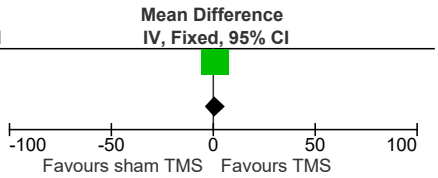


Figure 12: Quality of life at ≤3 months (SF-36 mental summary score, 0-100, high is good outcome, change scores)

Study or Subgroup	TMS Mean	TMS SD	TMS Total	Sham TMS Mean	Sham TMS SD	Sham TMS Total	Weight	Mean Difference IV, Fixed, 95% CI
Boyer 2014	5	6.9	16	-1.6	7.6	13	100.0%	6.60 [1.26, 11.94]
Total (95% CI)			**16**			**13**	**100.0%**	**6.60 [1.26, 11.94]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.42 (P = 0.02)

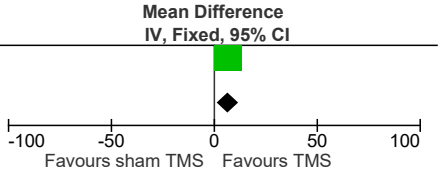


Figure 13: Quality of life at ≤3 months (WHOQOL-BREF physical domain, 4-20, high is good outcome, final values)

Study or Subgroup	TMS Mean	TMS SD	TMS Total	Sham TMS Mean	Sham TMS SD	Sham TMS Total	Weight	Mean Difference IV, Fixed, 95% CI
Tekin 2014	14.6	2.52	27	11.33	2.84	24	100.0%	3.27 [1.79, 4.75]
Total (95% CI)			**27**			**24**	**100.0%**	**3.27 [1.79, 4.75]**

Heterogeneity: Not applicable
Test for overall effect: Z = 4.33 (P < 0.0001)

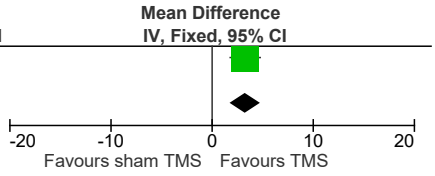


Figure 14: Quality of life at ≤3 months (WHOQOL-BREF psychological domain, 4-20, high is good outcome, final values)

Study or Subgroup	TMS Mean	TMS SD	TMS Total	Sham TMS Mean	Sham TMS SD	Sham TMS Total	Weight	Mean Difference IV, Fixed, 95% CI
Tekin 2014	13.89	2.47	27	12.71	2.49	24	100.0%	1.18 [-0.18, 2.54]
Total (95% CI)			**27**			**24**	**100.0%**	**1.18 [-0.18, 2.54]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.70 (P = 0.09)

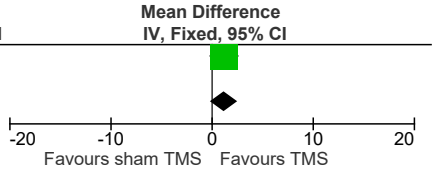


Figure 15: Quality of life at ≤3 months (FIQ, 0-100, high is poor outcome, final values)

Study or Subgroup	TMS Mean	TMS SD	TMS Total	Sham TMS Mean	Sham TMS SD	Sham TMS Total	Weight	Mean Difference IV, Fixed, 95% CI
Lee 2012	51.8	13.51	10	53.7	27.3	5	16.0%	-1.90 [-27.25, 23.45]
Short 2011	38.99	19.44	10	47.93	14.7	10	45.1%	-8.94 [-24.05, 6.17]
Yagci 2014	36.95	24.27	13	48.13	16.79	12	38.9%	-11.18 [-27.44, 5.08]
Total (95% CI)			**33**			**27**	**100.0%**	**-8.69 [-18.83, 1.46]**

Heterogeneity: Chi² = 0.37, df = 2 (P = 0.83); I² = 0%
Test for overall effect: Z = 1.68 (P = 0.09)

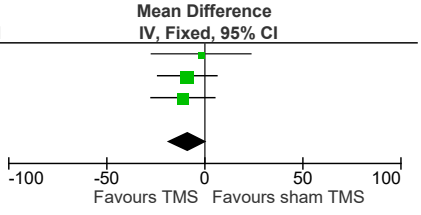
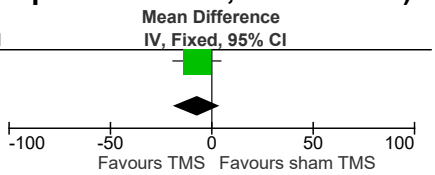


Figure 16: Quality of life at >3 months (FIQ, 0-100, high is poor outcome, final values)

Study or Subgroup	TMS Mean	TMS SD	TMS Total	Sham TMS Mean	Sham TMS SD	Sham TMS Total	Weight	Mean Difference IV, Fixed, 95% CI
Mhalla 2011	56	17.7	15	63.3	15	15	100.0%	-7.30 [-19.04, 4.44]
Total (95% CI)			**15**			**15**	**100.0%**	**-7.30 [-19.04, 4.44]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.22 (P = 0.22)

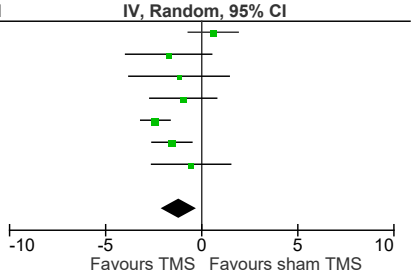


1

Figure 17: Pain reduction at ≤3 months (VAS, McGill Pain questionnaire, 0-10, high is poor outcome, final values)

Study or Subgroup	TMS Mean	TMS SD	TMS Total	Sham TMS Mean	Sham TMS SD	Sham TMS Total	Weight	Mean Difference IV, Random, 95% CI
Carretero 2009	8.1	1	14	7.5	2.1	12	16.7%	0.60 [-0.70, 1.90]
Dall'Agnol 2014	3.57	2.82	12	5.29	2.78	12	10.2%	-1.72 [-3.96, 0.52]
Lee 2012	6.05	2.23	10	7.23	2.53	5	8.4%	-1.18 [-3.79, 1.43]
Short 2011	4.41	1.95	10	5.37	2.02	10	13.3%	-0.96 [-2.70, 0.78]
Tekin 2014	3.796	0.983	27	6.208	1.668	24	21.2%	-2.41 [-3.18, -1.65]
Umezaki 2016	1.33	0.78	12	2.88	1.36	8	18.9%	-1.55 [-2.59, -0.51]
Yagci 2014	4.75	2.76	13	5.3	2.49	12	11.2%	-0.55 [-2.61, 1.51]
Total (95% CI)			**98**			**83**	**100.0%**	**-1.17 [-2.10, -0.24]**

Heterogeneity: Tau² = 0.91; Chi² = 16.82, df = 6 (P = 0.010); I² = 64%
Test for overall effect: Z = 2.46 (P = 0.01)

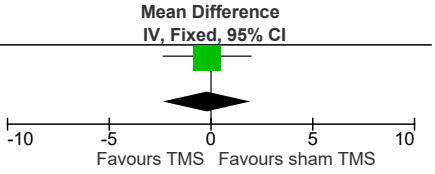


2

Figure 18: Physical function at ≤3 months (BPI functional impairment subscale, 0-10, high is poor outcome, final values)

Study or Subgroup	TMS Mean	TMS SD	TMS Total	Sham TMS Mean	Sham TMS SD	Sham TMS Total	Weight	Mean Difference IV, Fixed, 95% CI
Short 2011	3.6	2.18	10	3.79	2.69	10	100.0%	-0.19 [-2.34, 1.96]
Total (95% CI)			**10**			**10**	**100.0%**	**-0.19 [-2.34, 1.96]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.17 (P = 0.86)

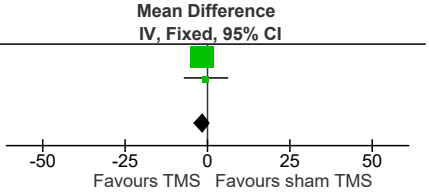


3

Figure 19: Psychological distress at ≤3 months (Beck depression inventory, 0-61, high is poor outcome, final values and change scores)

Study or Subgroup	TMS Mean	TMS SD	TMS Total	Sham TMS Mean	Sham TMS SD	Sham TMS Total	Weight	Mean Difference IV, Fixed, 95% CI
Boyer 2014	-1.9	2.8	16	-0.1	4.4	13	84.8%	-1.80 [-4.56, 0.96]
Lee 2012	17.85	6.553	10	18.3	5.8	5	15.2%	-0.45 [-6.96, 6.06]
Total (95% CI)			**26**			**18**	**100.0%**	**-1.59 [-4.13, 0.94]**

Heterogeneity: Chi² = 0.14, df = 1 (P = 0.71); I² = 0%
Test for overall effect: Z = 1.23 (P = 0.22)

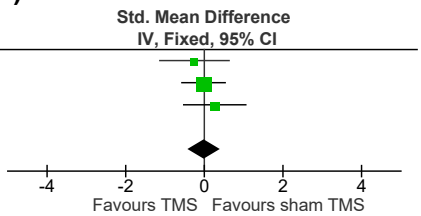


4

Figure 20: Psychological distress at ≤3 months (Hamilton depression rating scale, MADRS, BDI, high is poor outcome, final values)

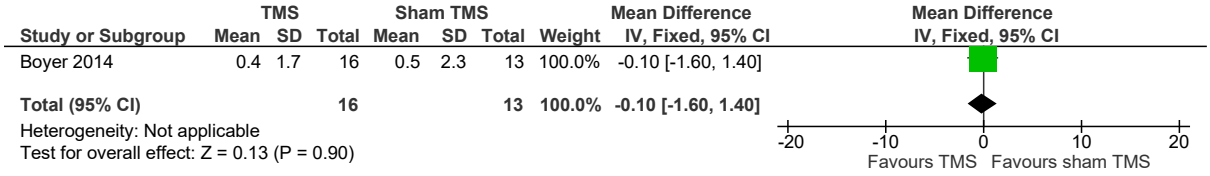
Study or Subgroup	TMS Mean	TMS SD	TMS Total	Sham TMS Mean	Sham TMS SD	Sham TMS Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Short 2011	14.1	9.42	10	16.4	8.18	10	20.8%	-0.25 [-1.13, 0.63]
Tekin 2014	10.14	3.96	27	10.24	6	24	53.3%	-0.02 [-0.57, 0.53]
Yagci 2014	16.75	10.6	13	14.15	8	12	25.9%	0.27 [-0.52, 1.05]
Total (95% CI)			**50**			**46**	**100.0%**	**0.01 [-0.39, 0.41]**

Heterogeneity: Chi² = 0.75, df = 2 (P = 0.69); I² = 0%
Test for overall effect: Z = 0.03 (P = 0.97)



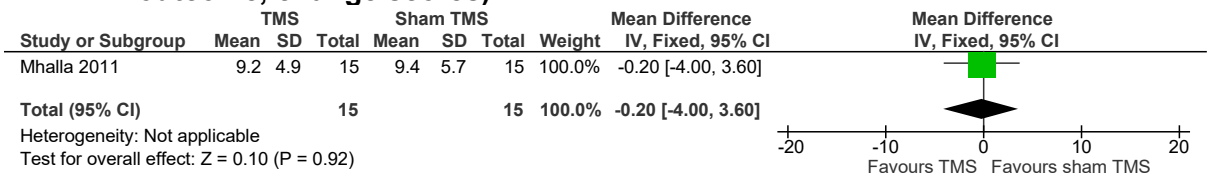
5

Figure 21: Psychological distress at ≤3 months (HADS anxiety, 0-21, high is poor outcome, change scores)



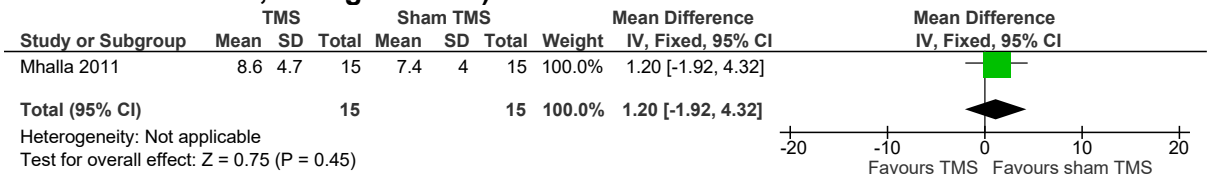
1

Figure 22: Psychological distress at >3 months (HADS anxiety, 0-21, high is poor outcome, change scores)



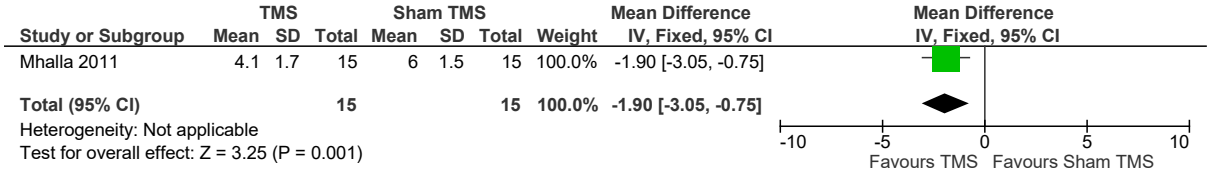
2

Figure 23: Psychological distress at >3 months (HADS depression, 0-21, high is poor outcome, change scores)



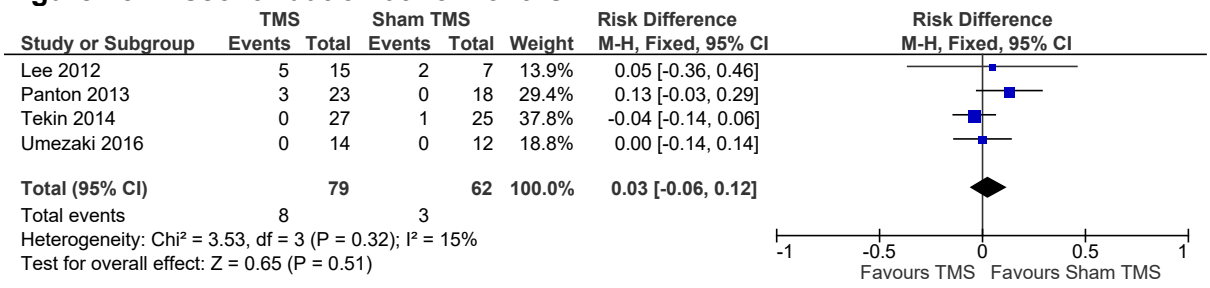
3

Figure 24: Pain interference at >3 months (BPI pain interference, 0-10, high is poor outcome, final values)



4

Figure 25: Discontinuation at ≤3 months

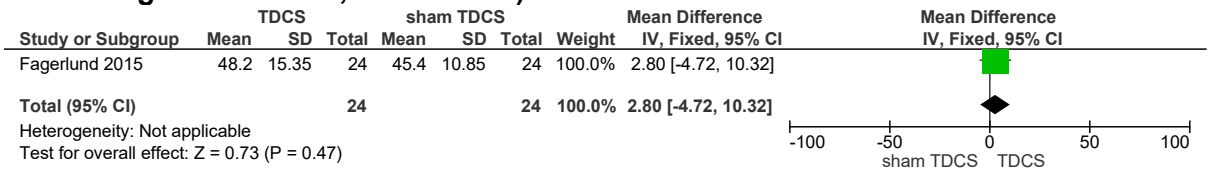


5

6

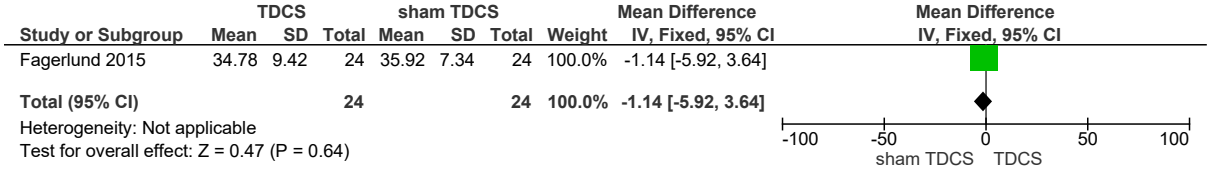
E.3 TDCS versus sham TDCS

Figure 26: Quality of life at ≤3 months (SF-36 mental summary score, 0-100, high is good outcome, final values)



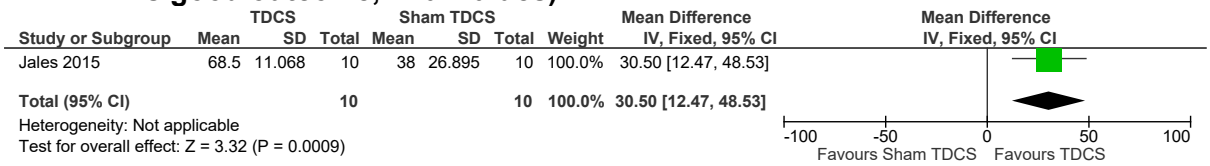
2

Figure 27: Quality of life at ≤3 months (SF-36 physical summary score, 0-100, high is good outcome, final values)



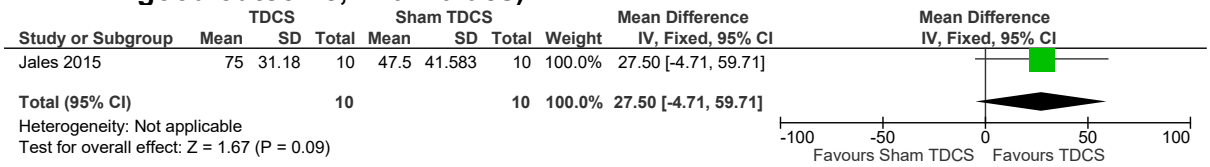
3

Figure 28: Quality of life at ≤3 months (SF-36 physical function subscale, 0-100, high is good outcome, final values)



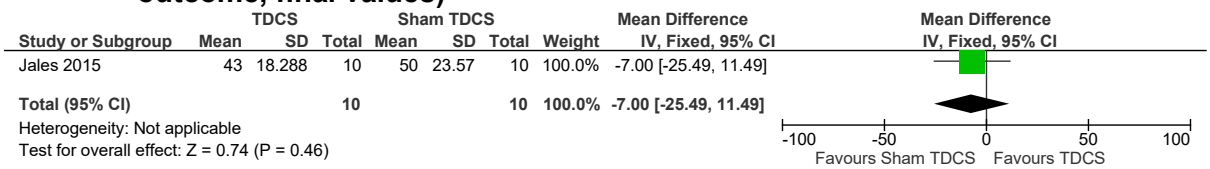
4

Figure 29: Quality of life at ≤3 months (SF-36 physical role subscale, 0-100, high is good outcome, final values)



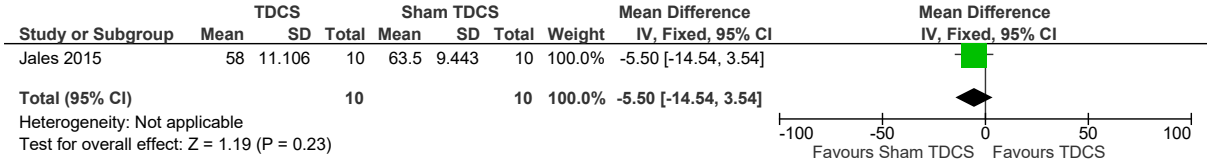
5

Figure 30: Quality of life at ≤3 months (SF-36 bodily pain subscale, 0-100, high is good outcome, final values)



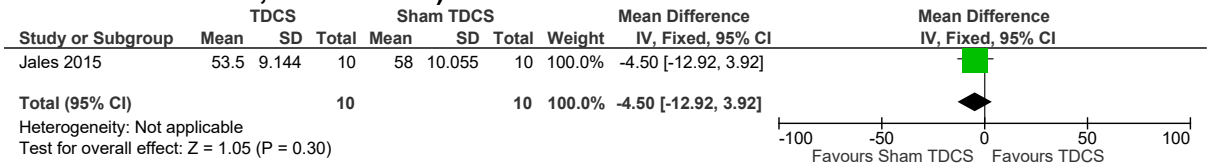
6

Figure 31: Quality of life at ≤3 months (SF-36 general health subscale, 0-100, high is good outcome, final values)



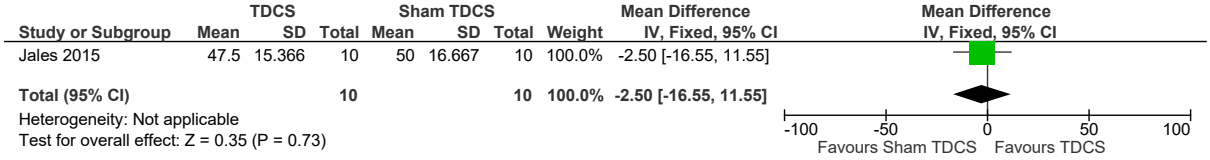
1

Figure 32: Quality of life at ≤3 months (SF-36 vitality subscale, 0-100, high is good outcome, final values)



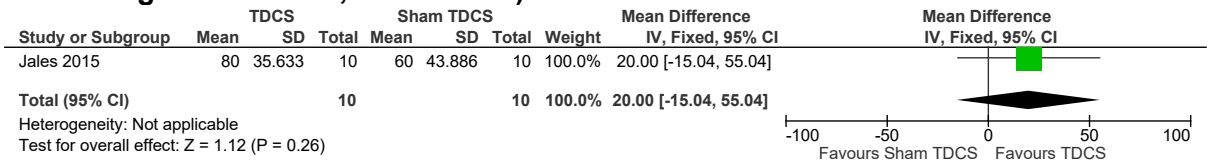
2

Figure 33: Quality of life at ≤3 months (SF-36 general aspects subscale, 0-100, high is good outcome, final values)



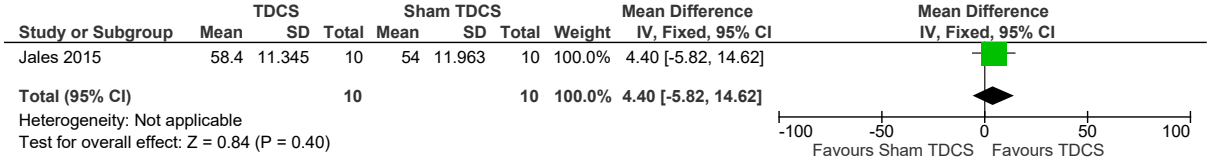
3

Figure 34: Quality of life at ≤3 months (SF-36 emotional role subscale, 0-100, high is good outcome, final values)



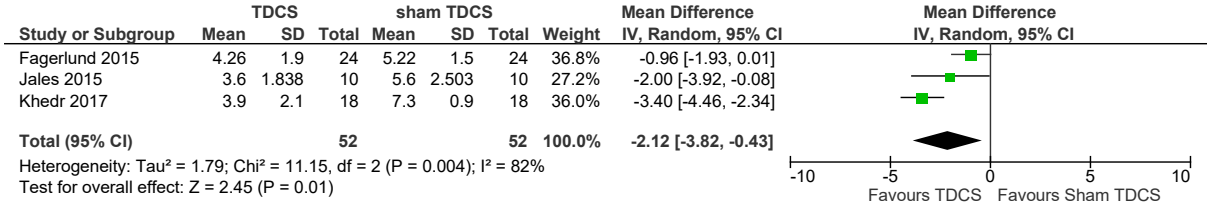
4

Figure 35: Quality of life at ≤3 months (SF-36 mental health subscale, 0-100, high is good outcome, final values)



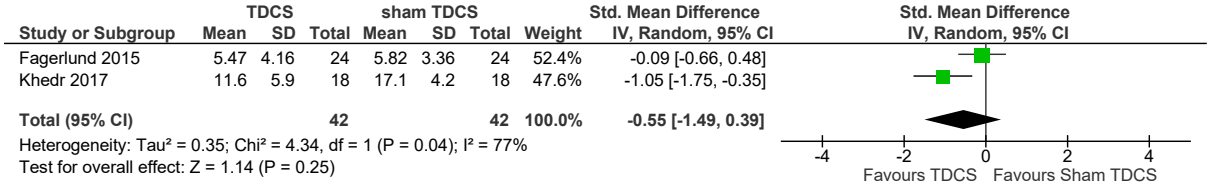
5

Figure 36: Pain reduction at ≤3 months (NRS, VAS, 0-10, high is poor outcome, final values)



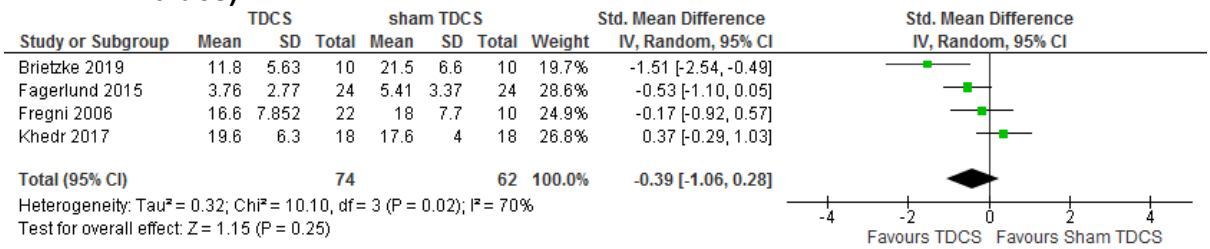
1

Figure 37: Psychological distress at ≤3 months (Hospital anxiety and depression scale, HAM-A, anxiety subscales, high is poor outcome, final values)



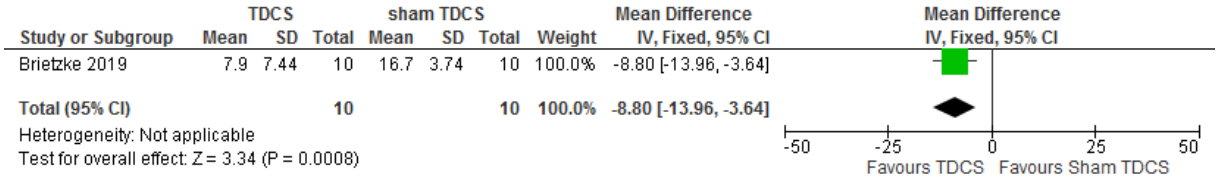
2

Figure 38: Psychological distress at ≤3 months (Hospital anxiety and depression scale, BDI, HAM-D, depression subscales, high is poor outcome, final values)



3

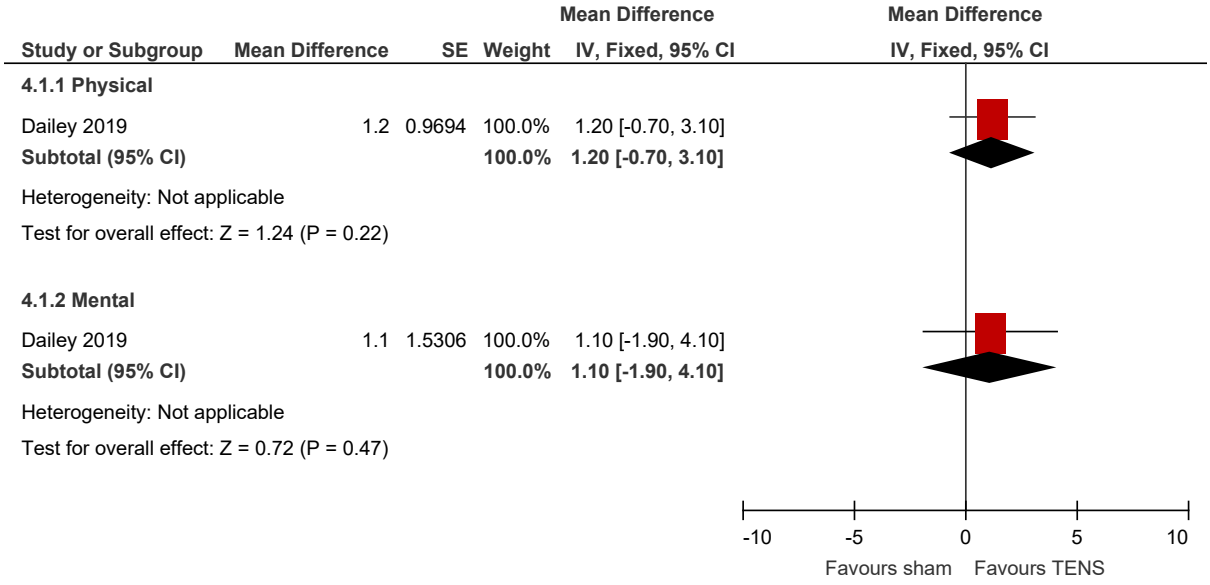
4 **Figure 39: Sleep at ≤3 months (PSQI, scale range not reported, high is poor outcome,**
5 **final values)**



6

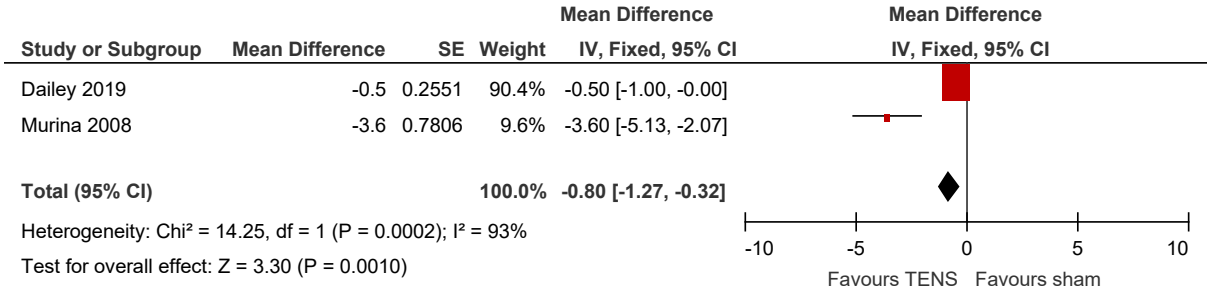
E.4 TENS versus sham TENS

Figure 40: Quality of life at ≤3 months (SF36 T scores, high is good outcome, change scores)



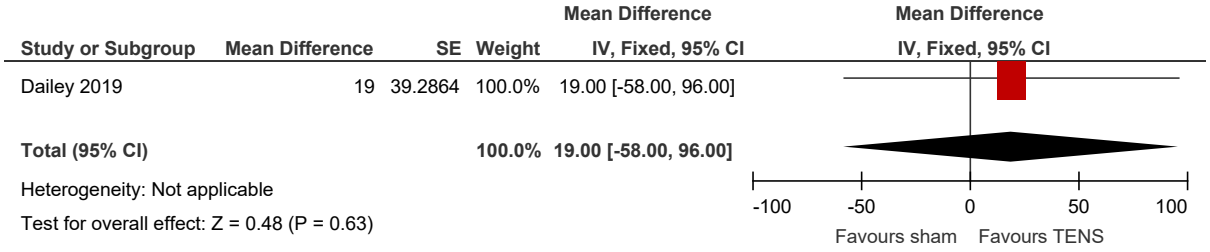
2

Figure 41: Pain reduction at ≤3 months (BPI, VAS, 0-10, high is poor outcome, final values and change scores)



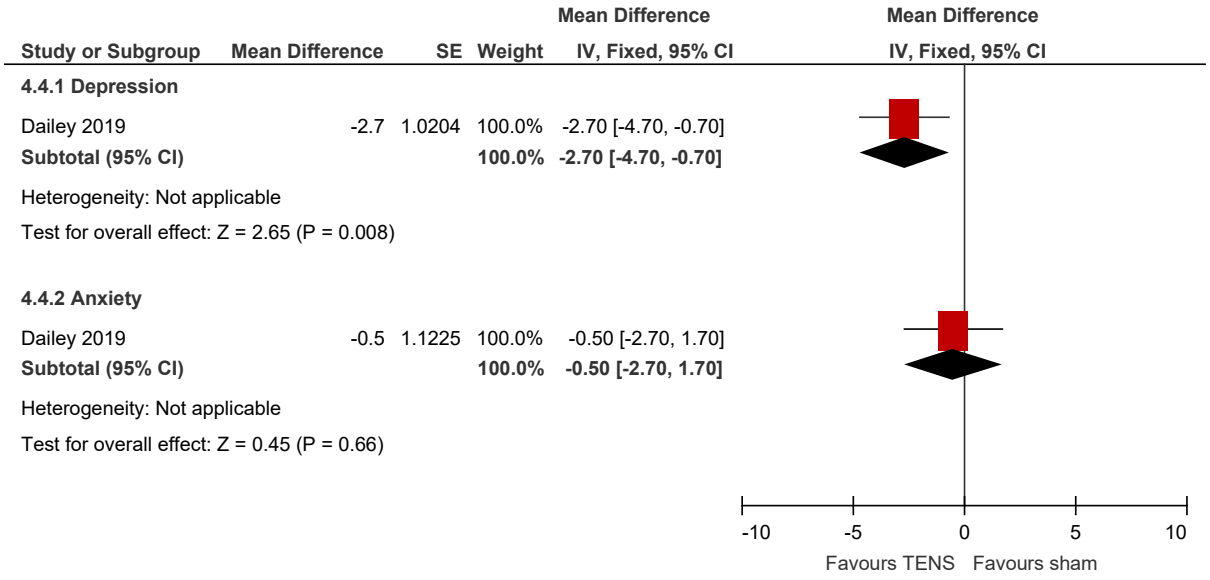
3

Figure 42: Physical function at ≤3 months (6 minute walk test, high is good outcome, change scores)



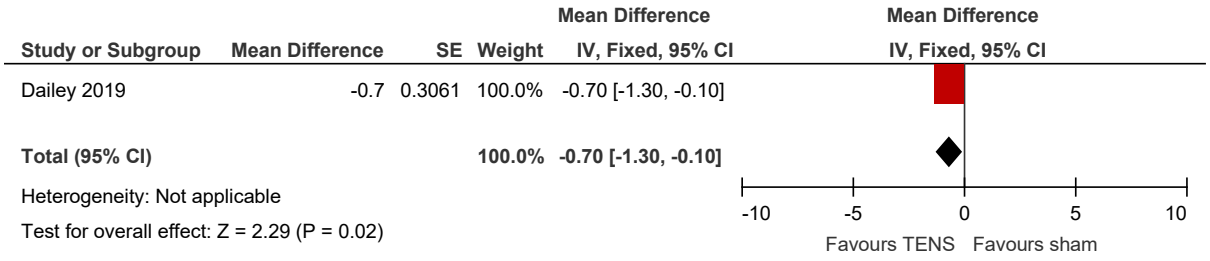
4

Figure 43: Psychological distress (PROMIS T scores, high is poor outcome, change scores)



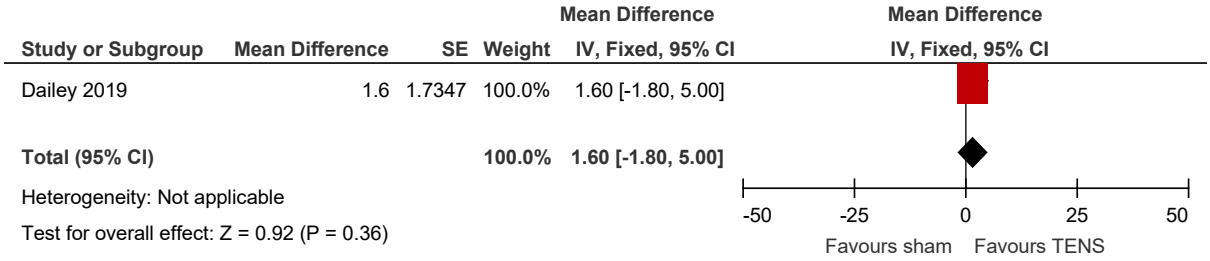
1

Figure 44: Pain interference at ≤3 months (BPI interference, 0-10, high is poor outcome, change scores)



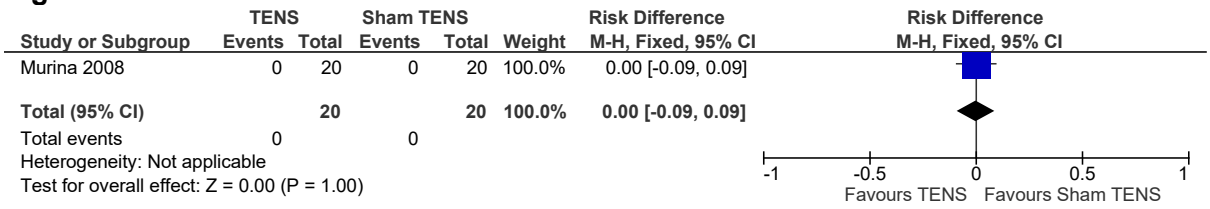
2

Figure 45: Pain self-efficacy at ≤3 months (Pain self-efficacy questionnaire, 0-60, high is good outcome, change scores)



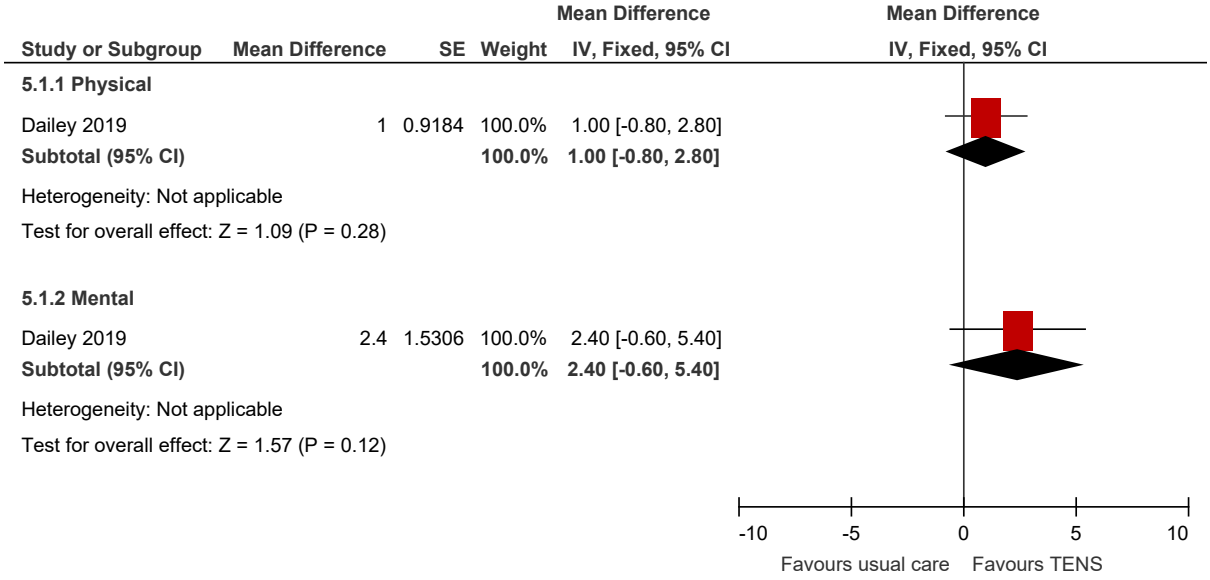
3

Figure 46: Discontinuation at ≤3 months



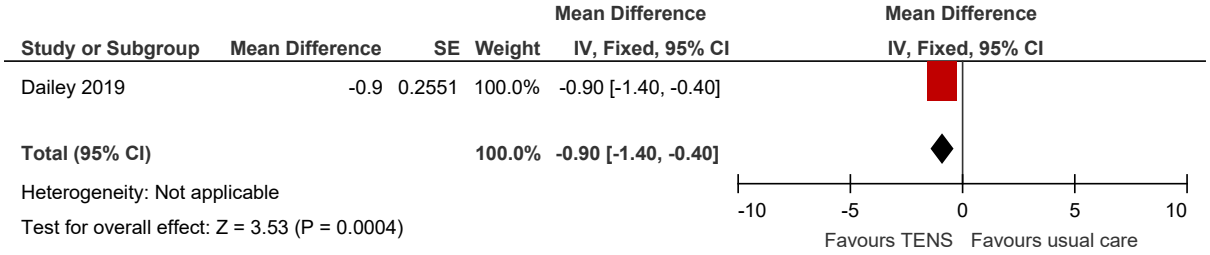
E.5 TENS versus usual care

Figure 47: Quality of life at ≤3 months (SF36 T scores, high is good outcome, change scores)



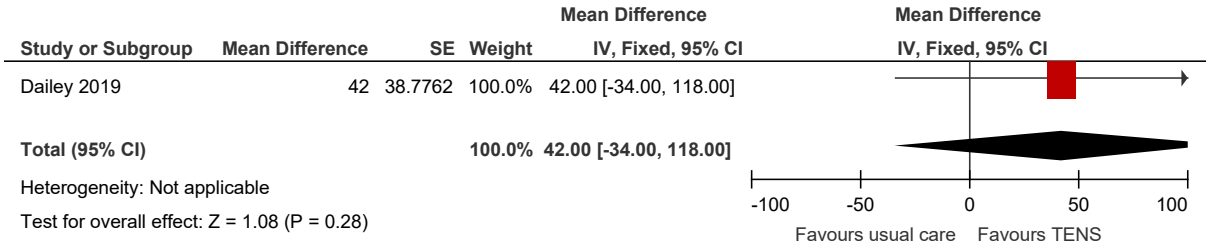
2

Figure 48: Pain reduction at ≤3 months (BPI, 0-10, high is poor outcome, change scores)



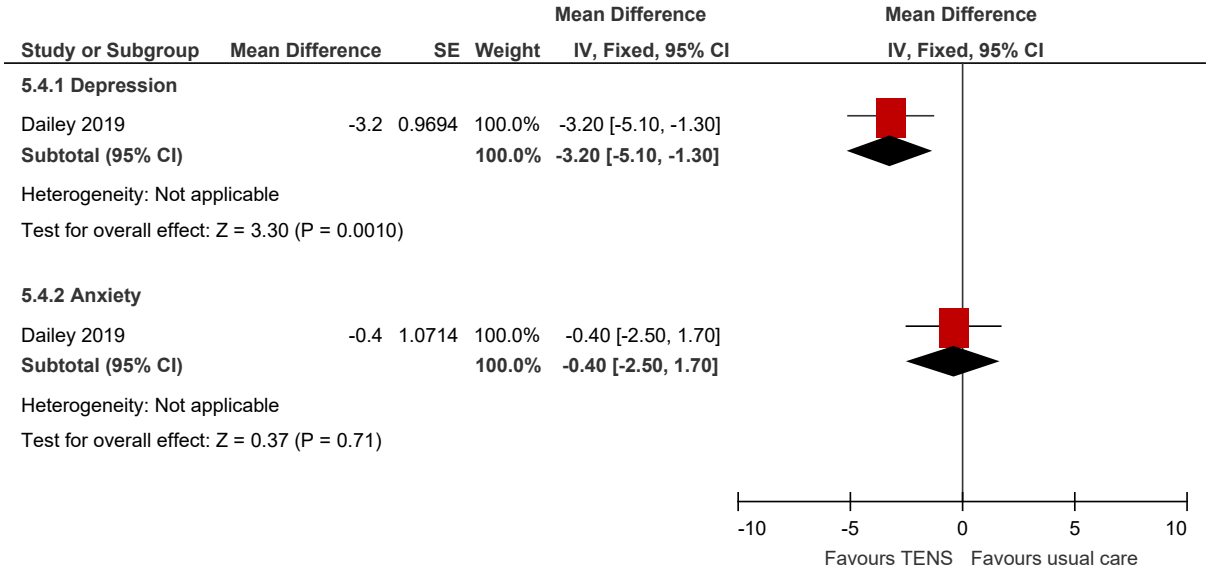
3

Figure 49: Physical function at ≤3 months (6 minute walk test, high is good outcome, change scores)



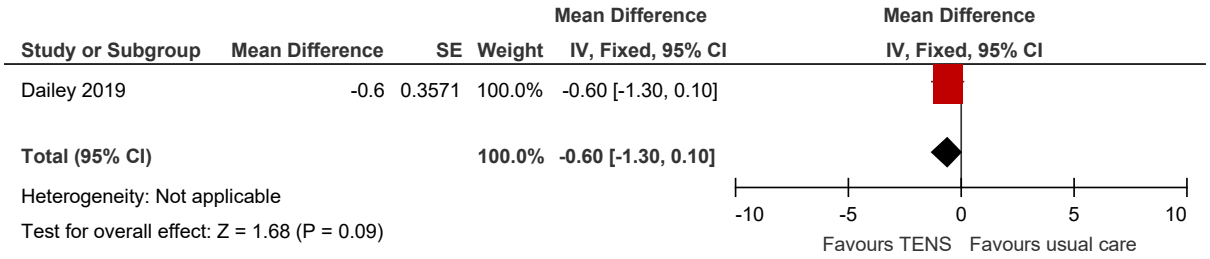
1

Figure 50: Psychological distress (PROMIS T scores, high is poor outcome, change scores)



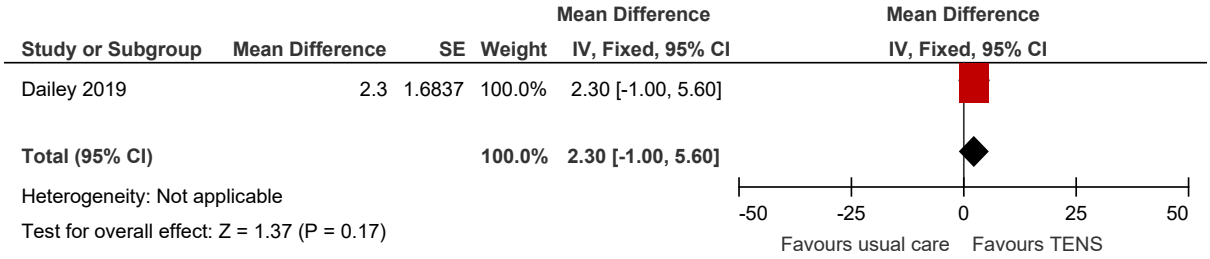
2

Figure 51: Pain interference at ≤3 months (BPI interference, 0-10, high is poor outcome, change scores)



3

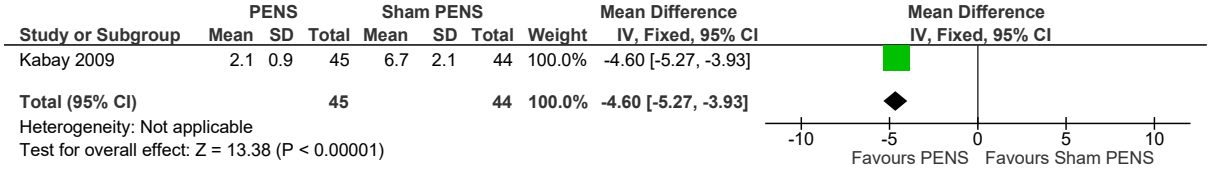
Figure 52: Pain self-efficacy at ≤3 months (Pain self-efficacy questionnaire, 0-60, high is good outcome, change scores)



1

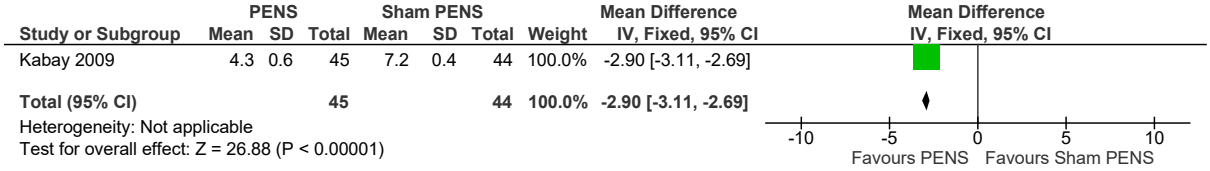
E.6 PENS versus sham PENS

Figure 53: Quality of life at ≤3 months (NIH-CPSI, 0-12, high is poor outcome, final values)



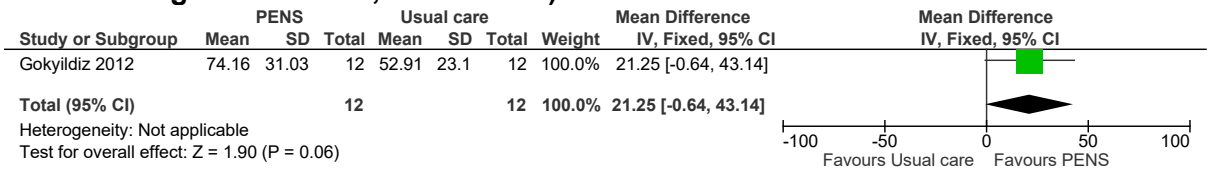
3

Figure 54: Pain reduction at ≤3 months (VAS, 0-10, high is poor outcome, final values)



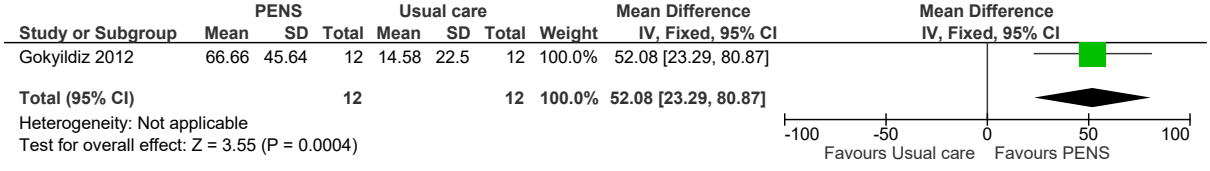
E.7 PENS versus usual care

Figure 55: Quality of life at ≤3 months (SF-36 physical function subscale, 0-100, high is good outcome, final values)



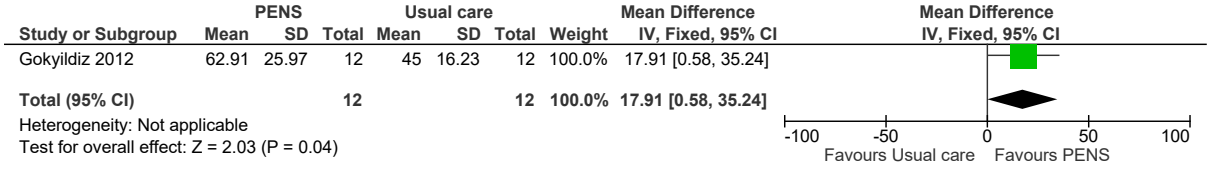
5

Figure 56: Quality of life at ≤3 months (SF-36 physical role subscale, 0-100, high is good outcome, final values)



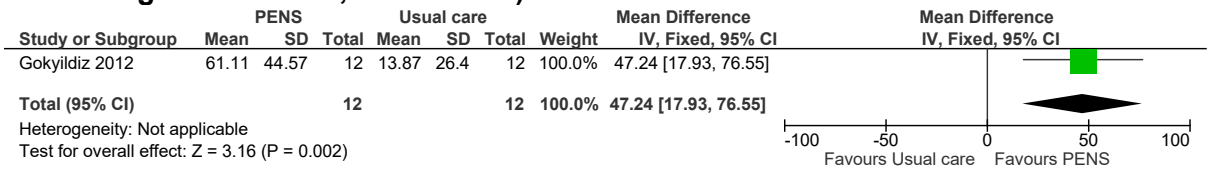
1

Figure 57: Quality of life at ≤3 months (SF-36 fatigue subscale, 0-100, high is good outcome, final values)



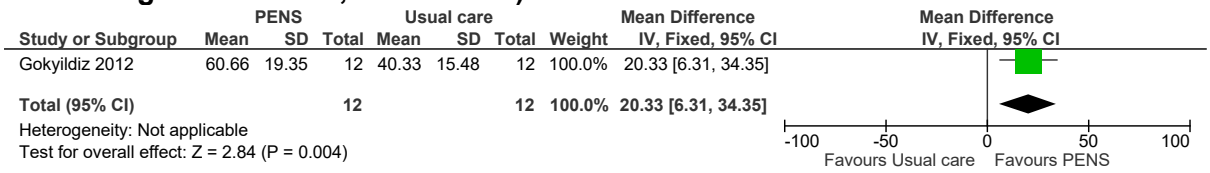
2

Figure 58: Quality of life at ≤3 months (SF-36 emotional role subscale, 0-100, high is good outcome, final values)



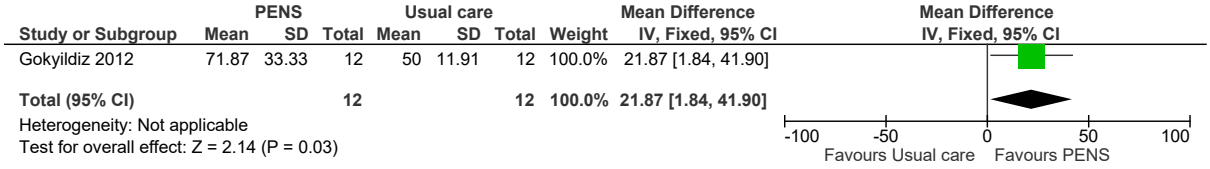
3

Figure 59: Quality of life at ≤3 months (SF-36 mental health subscale, 0-100, high is good outcome, final values)



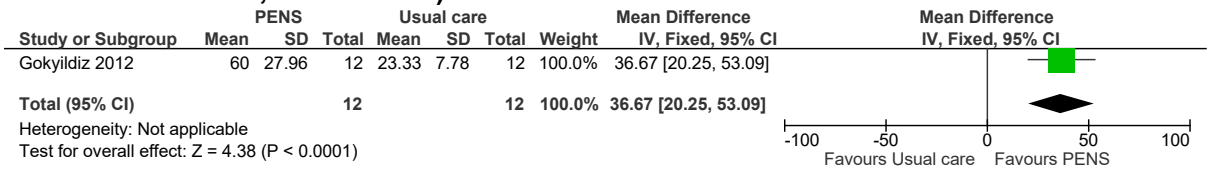
4

Figure 60: Quality of life at ≤3 months (SF-36 social functioning subscale, 0-100, high is good outcome, final values)



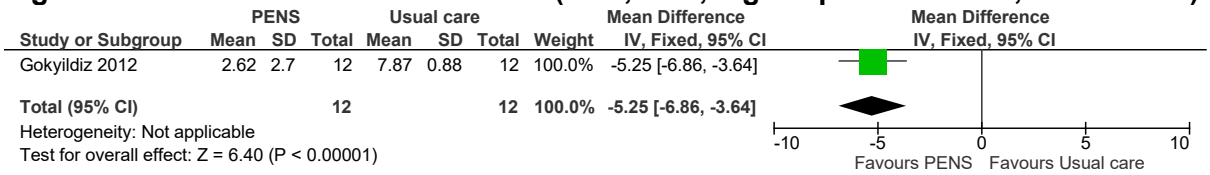
5

Figure 61: Quality of life at ≤3 months (SF-36 bodily pain subscale, 0-100, high is good outcome, final values)



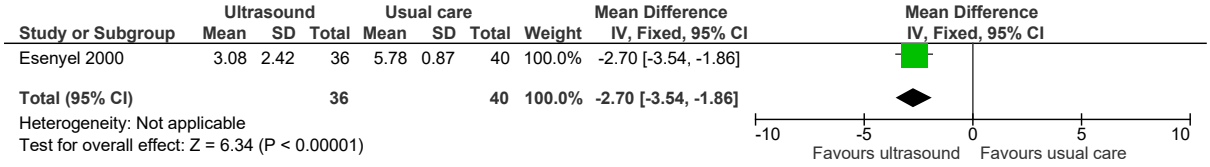
6

Figure 62: Pain reduction at ≤3 months (VAS, 0-10, high is poor outcome, final values)



E.8 Therapeutic ultrasound versus usual care

Figure 63: Pain reduction at 3 months (VAS, 0-10, high is poor outcome, final values)



Appendix F: GRADE tables

Table 15: Clinical evidence profile: Laser therapy versus sham laser therapy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Laser therapy	Control	Relative (95% CI)	Absolute		
Quality of life at 2 weeks-3 months (Oral health impact profile, FIQ, high is poor outcome, final values)												
6	randomised trials	serious[3]	serious[2]	no serious indirectness	serious[1]	none	159	117	-	SMD 0.68 lower (1.1 to 0.25 lower)	⊕OOO VERY LOW	CRITICAL
Quality of life at 3 months (SF-36 physical component summary score, 0-100, high is good outcome, change scores)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	55	55	-	MD 2.09 higher (0.91 lower to 5.09 higher)	⊕⊕⊕O MODERATE	CRITICAL
Quality of life at 3 months (SF-36 mental component summary score, 0-100, high is good outcome, change scores)												
2	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[1]	none	55	55	-	MD 0.74 lower (5.35 lower to 3.87 higher)	⊕⊕OO LOW	CRITICAL
Quality of life at 24 weeks (FIQ, 0-100, high is poor outcome, final values)												
2	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	59	58	-	SMD 0.78 lower (1.16 to 0.4 lower)	⊕⊕OO LOW	CRITICAL
Pain reduction at 1 week to 12 weeks (VAS, NRS, FIQ pain scale, high is poor outcome, 0-10, final values and change scores)												
13	randomised trials	serious[3]	serious[2]	no serious indirectness	serious[1]	none	301	257	-	MD 1.42 lower (2.12 to 0.73 lower)	⊕OOO VERY LOW	CRITICAL
Pain reduction at 14-16 weeks (VAS, high is poor outcome, 0-10, final values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	36	35	-	MD 0.6 lower (0.91 to 0.3 lower)	⊕⊕⊕O MODERATE	CRITICAL

Psychological distress at 4 weeks (Hospital anxiety and depression rating scale, anxiety subscale, 0-21, high is poor outcome, final values)											
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	32	12	-	MD 0.83 higher (1.52 lower to 3.18 higher)	⊕⊕OO LOW	CRITICAL
Psychological distress at 4 weeks (Hospital anxiety and depression rating scale, depression subscale, 0-21, high is poor outcome, final values)											
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	32	16	-	MD 1.29 higher (1.39 lower to 3.96 higher)	⊕⊕OO LOW	CRITICAL
Discontinuation at 3 months											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	2/45 (4.4%)	6.7%	RR 0.67 (0.12 to 3.8)	22 fewer per 1000 (from 59 fewer to 188 more)	⊕⊕OO LOW	IMPORTANT

1 *1 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.*
2 *2 Downgraded for heterogeneity, unexplained by subgroup analysis*
3 *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*
4 *bias*

5 **Table 16: Clinical evidence profile: TMS versus sham TMS**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**TMS**	**Control**	**Relative (95% CI)**	**Absolute**		
Quality of life at 10 weeks (SF-36 physical summary score, 0-100, high is good outcome, change scores)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	16	13	-	MD 1 higher (4.12 lower to 6.12 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life at 10 weeks (SF-36 mental summary score, 0-100, high is good outcome, change scores)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	16	13	-	MD 6.6 higher (1.26 to 11.94 higher)	⊕OOO VERY LOW	IMPORTANT
Quality of life at 2 weeks (WHOQOL-BREF physical domain, 4-20, high is good outcome, final values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	27	24	-	MD 3.27 higher (1.79 to 4.75 higher)	⊕⊕⊕⊕ HIGH	CRITICAL

Quality of life at 2 weeks (WHOQOL-BREF psychological domain, 4-20, high is good outcome, final values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	27	24	-	MD 1.18 higher (0.18 lower to 2.54 higher)	⊕⊕⊕O MODERATE	CRITICAL
Quality of life at 4 weeks -3 months (FIQ, 0-100, high is poor outcome, final values)												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	33	27	-	MD 8.69 lower (18.83 lower to 1.46 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life at 25 weeks (FIQ, 0-100, high is poor outcome, final values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15	15	-	MD 7.3 lower (19.04 lower to 4.44 higher)	⊕OOO VERY LOW	CRITICAL
Pain reduction at 2 weeks -3 months (VAS, McGill Pain questionnaire, 0-10, high is poor outcome, final values)												
7	randomised trials	serious[1]	serious[3]	no serious indirectness	serious[2]	none	98	83	-	MD 1.17 lower (2.1 to 0.24 lower)	⊕OOO VERY LOW	CRITICAL
Physical function at 4 weeks (BPI functional impairment subscale, 0-10, high is poor outcome, final values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10	10	-	MD 0.19 lower (2.34 lower to 1.96 higher)	⊕OOO VERY LOW	CRITICAL
Psychological distress at 6-10 weeks (Beck depression inventory, 0-61, high is poor outcome, final values and change scores)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	26	18	-	MD 1.59 lower (4.13 lower to 0.94 higher)	⊕OOO VERY LOW	CRITICAL
Psychological distress at 2 weeks -3 months (Hamilton depression rating scale, MADRS, BDI, high is poor outcome, final values)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	50	46	-	SMD 0.01 higher (0.39 lower to 0.41 higher)	⊕⊕⊕O MODERATE	CRITICAL
Psychological distress at 10 weeks (HADS anxiety, 0-21, high is poor outcome, change scores)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	16	13	-	MD 0.1 lower (1.6 lower to 1.4 higher)	⊕OOO VERY LOW	CRITICAL
Psychological distress at 25 weeks (HADS anxiety, 0-21, high is poor outcome, change scores)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	15	15	-	MD 0.2 lower (4 lower to 3.6 higher)	⊕OOO VERY LOW	CRITICAL
Psychological distress at 25 weeks (HADS depression, 0-21, high is poor outcome, change scores)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15	15	-	MD 1.2 higher (1.92 lower to 4.32 higher)	⊕OOO VERY LOW	CRITICAL
Pain interference at 25 weeks (BPI pain interference, 0-10, high is poor outcome, final values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15	15	-	MD 1.9 lower (3.05 to 0.75 lower)	⊕OOO VERY LOW	CRITICAL
Discontinuation at 2-6 weeks (follow-up 2-6 weeks)												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	8/79 (10.1%)	2%	RD 0.03 (-0.06 to 0.12)	12 more per 1000 (from 25 fewer to 50 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 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

3 Downgraded for heterogeneity, unexplained by subgroup analysis

Table 17: Clinical evidence profile: TDCS versus sham TDCS

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**TDCS**	**Control**	**Relative (95% CI)**	**Absolute**		
Quality of life at 4 weeks (SF-36 mental summary score, 0-100, high is good outcome, final values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	24	24	-	MD 2.8 higher (4.72 lower to 10.32 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life at 4 weeks (SF-36 physical summary score, 0-100, high is good outcome, final values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	24	24	-	MD 1.14 lower (5.92 lower to 3.64 higher)	⊕OOO VERY LOW	CRITICAL

Quality of life at 10 weeks (SF-36 physical function subscale, 0-100, high is good outcome, final values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	10	10	-	MD 30.5 higher (12.47 to 48.53 higher)	⊕⊕⊕O MODERATE	CRITICAL
Quality of life at 10 weeks (SF-36 physical role subscale, 0-100, high is good outcome, final values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10	10	-	MD 27.5 higher (4.71 lower to 59.71 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life at 10 weeks (SF-36 bodily pain subscale, 0-100, high is good outcome, final values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10	10	-	MD 7 lower (25.49 lower to 11.49 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life at 10 weeks (SF-36 general health subscale, 0-100, high is good outcome, final values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10	10	-	MD 5.5 lower (14.54 lower to 3.54 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life at 10 weeks (SF-36 vitality subscale, 0-100, high is good outcome, final values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10	10	-	MD 4.5 lower (12.92 lower to 3.92 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life at 10 weeks (SF-36 general aspects subscale, 0-100, high is good outcome, final values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10	10	-	MD 2.5 lower (16.55 lower to 11.55 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life at 10 weeks (SF-36 emotional role subscale, 0-100, high is good outcome, final values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10	10	-	MD 20 higher (15.04 lower to 55.04 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life at 10 weeks (SF-36 mental health subscale, 0-100, high is good outcome, final values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10	10	-	MD 4.4 higher (5.82 lower to 14.62 higher)	⊕OOO VERY LOW	CRITICAL
Pain reduction at 4-10 weeks (NRS, VAS, 0-10, high is poor outcome, final values)												

3	randomised trials	serious[1]	serious[3]	no serious indirectness	serious[2]	none	52	52	-	MD 2.12 lower (3.82 to 0.43 lower)	⊕OOO VERY LOW	CRITICAL
Psychological distress at 4-8 weeks (Hospital anxiety and depression scale, HAM-A, anxiety subscales, high is poor outcome, final values)												
2	randomised trials	serious[1]	serious[3]	no serious indirectness	serious[2]	none	42	42	-	SMD 0.55 lower (1.49 lower to 0.39 higher)	⊕OOO VERY LOW	CRITICAL
Psychological distress at 3-12 weeks (Hospital anxiety and depression scale, BDI, HAM-D, depression subscales, high is poor outcome, final values)												
4	randomised trials	serious[1]	serious[3]	no serious indirectness	serious[2]	none	74	62	-	SMD 0.39 lower (1.06 lower to 0.28 higher)	⊕OOO VERY LOW	CRITICAL
Sleep at ≤3 months (PSQI, scale range not reported, high is poor outcome, final values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	10	10	-	MD 8.8 lower (13.96 to 3.64 lower)	⊕⊕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 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

3 Downgraded for heterogeneity, unexplained by subgroup analysis

Table 18: Clinical evidence profile: TENS versus sham TENS

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**TENS**	**Control**	**Relative (95% CI)**	**Absolute**		
Quality of life at 4 weeks (SF36 physical T scores, high is good outcome, change scores)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	103	99	-	MD 1.2 higher (0.7 lower to 3.1 higher)	⊕⊕⊕O MODERATE	CRITICAL
Quality of life at 4 weeks (SF36 mental T scores, high is good outcome, change scores)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	103	99	-	MD 1.1 higher (1.9 lower to 4.1 higher)	⊕⊕⊕O MODERATE	CRITICAL
Pain reduction at 4-10 weeks (BPI, VAS, 0-10, high is poor outcome, final values)												

2	randomised trials	serious[1]	very serious inconsistency[2]	no serious indirectness	serious[3]	none	123	119	-	MD 0.8 lower (1.27 to 0.32 lower)	⊕OOO VERY LOW	CRITICAL
Physical function at 4 weeks (6 minute walk test, change scores)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	103	99	-	MD 19 higher (58 lower to 96 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Psychological distress at 4 weeks (PROMIS depression T scores, high is poor outcome, change scores)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	103	99	-	MD 2.7 lower (4.7 to 0.7 lower)	⊕⊕OO LOW	CRITICAL
Psychological distress at 4 weeks (PROMIS anxiety T scores, high is poor outcome, change scores)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	103	99	-	MD 0.5 lower (2.7 lower to 1.7 higher)	⊕⊕⊕O MODERATE	CRITICAL
Pain interference (Brief pain inventory interference, 0-10, high is poor outcome, change scores)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	103	99	-	MD 0.7 lower (1.3 to 0.1 lower)	⊕⊕OO LOW	CRITICAL
Pain self-efficacy (Pain self-efficacy questionnaire, 0-60, high is good outcome, change scores)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	103	99	-	MD 1.6 higher (1.8 lower to 5 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Discontinuation at 10 weeks												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	0/20 (0%)	0%	RD 0 (-0.09 to 0.09)	0 fewer per 1000 (from 90 fewer to 90 more)	⊕⊕OO LOW	CRITICAL

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 for heterogeneity, unexplained by subgroup analysis

3 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 19: Clinical evidence profile: TENS versus usual care

Quality assessment							No of patients		Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TENS	Control	Relative (95% CI)	Absolute		
Quality of life at 4 weeks (SF36 physical T scores, high is good outcome, change scores)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	103	99	-	MD 1 higher (0.8 lower to 2.8 higher)	⊕⊕⊕O MODERATE	CRITICAL
Quality of life at 4 weeks (SF36 mental T scores, high is good outcome, change scores)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	103	99	-	MD 2.4 higher (0.6 lower to 5.4 higher)	⊕⊕OO LOW	CRITICAL
Pain reduction at 10 weeks (BPI, 0-10, high is poor outcome, final values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	103	99	-	MD 0.9 lower (1.4 to 0.4 lower)	⊕⊕OO LOW	CRITICAL
Physical function at 4 weeks (6 minute walk test, change scores)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	103	99	-	MD 42 higher (34 lower to 118 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Psychological distress at 4 weeks (PROMIS depression T scores, high is poor outcome, change scores)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	103	99	-	MD 3.2 lower (5.1 to 1.3 lower)	⊕⊕OO LOW	CRITICAL
Psychological distress at 4 weeks (PROMIS anxiety T scores, high is poor outcome, change scores)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	103	99	-	MD 0.4 lower (2.5 lower to 1.7 higher)	⊕⊕⊕O MODERATE	CRITICAL
Pain interference (Brief pain inventory interference, 0-10, high is poor outcome, change scores)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	103	99	-	MD 0.6 lower (1.3 lower to 0.1 higher)	⊕⊕OO LOW	CRITICAL
Pain self-efficacy (Pain self-efficacy questionnaire, 0-60, high is good outcome, change scores)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	103	99	-	MD 2.3 higher (1 lower to 5.6 higher)	⊕⊕⊕⊕ HIGH	CRITICAL

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 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 20: Clinical evidence profile: PENS versus sham PENS

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PENS	Control	Relative (95% CI)	Absolute		
Quality of life at 3 months (NIH-CPSI, 0-12, high is poor outcome, final values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	45	44	-	MD 4.6 lower (5.27 to 3.93 lower)	⊕⊕OO LOW	CRITICAL
Pain reduction at 3 months (VAS, 0-10, high is poor outcome, final values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	45	44	-	MD 2.9 lower (3.11 to 2.69 lower)	⊕⊕OO LOW	CRITICAL

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

Table 21: Clinical evidence profile: PENS versus usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PENS	Control	Relative (95% CI)	Absolute		
Quality of life at 3 months (SF-36 physical function, 0-100, high is good outcome, final values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12	12	-	MD 21.25 higher (0.64 lower to 43.14 higher)	⊕OOO VERY LOW	CRITICAL

Quality of life at 3 months (SF-36 physical role, 0-100, high is good outcome, final values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12	12	-	MD 52.08 higher (23.29 to 80.87 higher)	⊕⊕OO LOW	CRITICAL
Quality of life at 3 months (SF-36 fatigue, 0-100, high is good outcome, final values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12	12	-	MD 17.91 higher (0.58 to 35.24 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life at 3 months (SF-36 emotional role, 0-100, high is good outcome, final values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12	12	-	MD 47.24 higher (17.93 to 76.55 higher)	⊕⊕OO LOW	CRITICAL
Quality of life at 3 months (SF-36 mental health, 0-100, high is good outcome, final values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12	12	-	MD 20.33 higher (6.31 to 34.35 higher)	⊕⊕OO LOW	CRITICAL
Quality of life at 3 months (SF-36 social functioning, 0-100, high is good outcome, final values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12	12	-	MD 21.87 higher (1.84 to 41.9 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life at 3 months (SF-36 bodily pain, 0-100, high is good outcome, final values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12	12	-	MD 36.67 higher (20.25 to 53.09 higher)	⊕⊕OO LOW	CRITICAL
Pain reduction at 3 months (VAS, 0-10, high is poor outcome, final values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12	12	-	MD 5.25 lower (6.86 to 3.64 lower)	⊕⊕OO LOW	CRITICAL

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 1 MID or by 2 increments if the confidence interval crossed both MIDs.

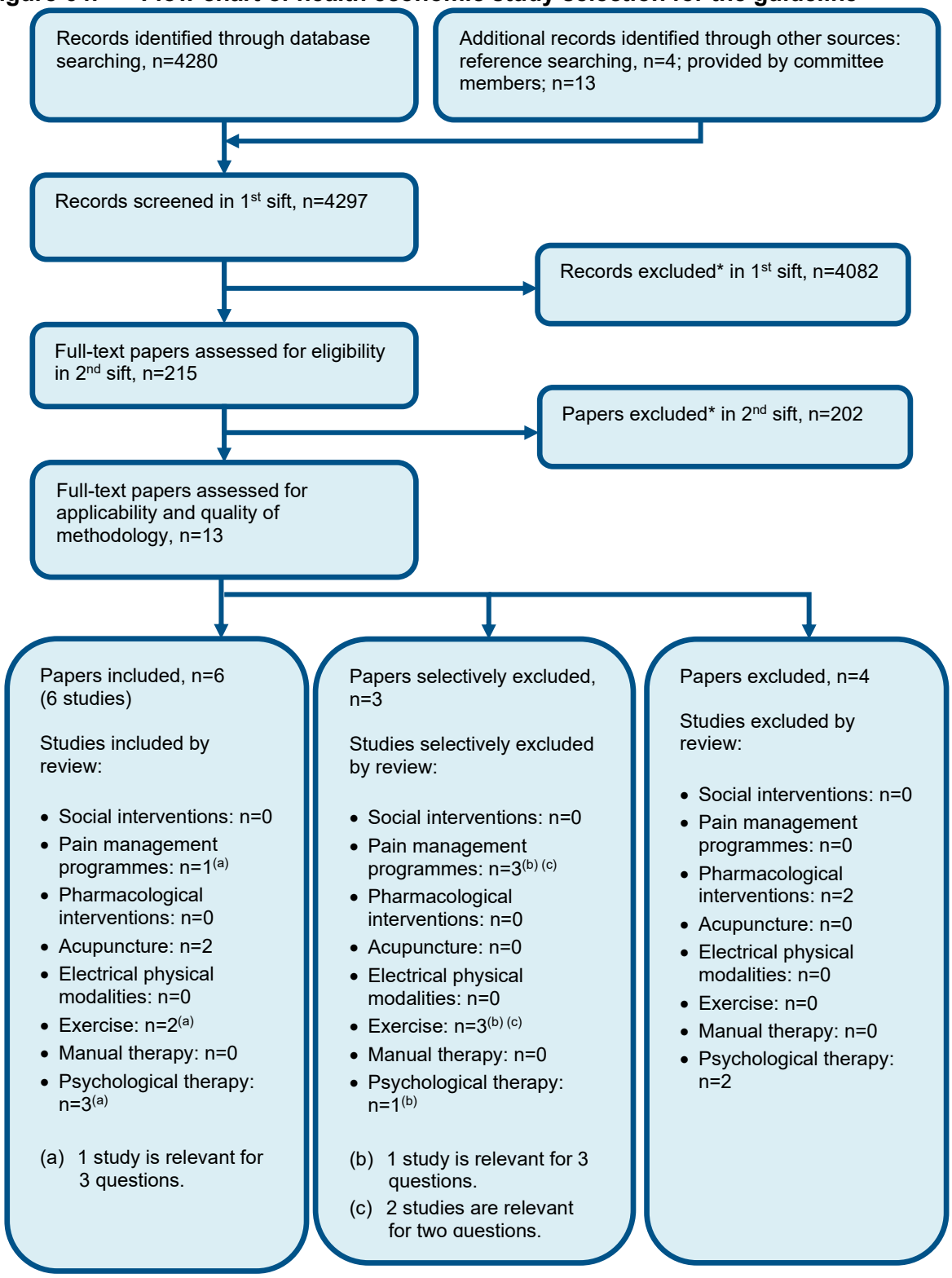
Table 22: Clinical evidence profile: Ultrasound versus sham ultrasound

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Therapeutic ultrasound	Control	Relative (95% CI)	Absolute		
Pain reduction at 3 months (VAS, 0-10, high is poor outcome, final values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	36	40	-	MD 2.7 lower (3.54 to 1.86 lower)	⊕⊕OO LOW	CRITICAL

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

Appendix G: Health economic evidence selection

Figure 64: Flow chart of health economic study selection for the guideline



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

1

Appendix H: Health economic evidence tables

None.

1 Appendix I: Excluded studies

I.1 Excluded clinical studies

3 **Table 23: Studies excluded from the clinical review**

Study	Exclusion reason
Aarskog 2007[1]	Incorrect population
Abdulla 2013[2]	Incorrect study design
Abram 1976[3]	Not guideline condition. Incorrect population
Abtahi 2018[4]	Not guideline condition. Incorrect population
Acedo 2015[5]	Not guideline condition. Incorrect population
Adrian 2014[6]	Abstract
Ahmed 2011[7]	Not guideline condition. Incorrect population
Ahsin 2009[8]	Incorrect interventions. Incorrect population
Akturk 2013[9]	Incorrect study design
Akturk 2018[10]	Inappropriate comparison
Alayat 2016[13]	Incorrect interventions (combinations of interventions; intervention combined with exercise)
Alayat 2017[12]	Incorrect interventions (combinations of interventions; intervention combined with exercise)
Albornoz-cabello 2017[14]	Incorrect population. Not guideline condition
Allais 2003[15]	Not guideline condition. Incorrect population
Al-maweri 2017[11]	Incorrect study design
Almay 1985[16]	Incorrect population. Incorrect population
Almeida 2003[18]	Incorrect interventions. Combined treatments (ultrasound plus interferential current)
Almeida 2018[17]	Incorrect population. Inappropriate comparison
Altas 2019 [20]	Incorrect intervention (both interventions combined with exercise programme)
Amanat 2013[21]	Incorrect interventions. Combined treatments (laser plus pharmacological)
Anderssonn 1976[22]	Incorrect population
Andrade ortega 2014[23]	Incorrect interventions
Andre-obadia 2006[24]	Incorrect population.
Anon 2003[366]	Not article
Anon 2004[300]	Abstract
Anon 2017[119]	Incorrect study design
Anonymous 2016[56]	Incorrect interventions. Incorrect study design
Anonymous 2017[25]	Incorrect interventions. Combined treatments
Ansari 2013[26]	Abstract
Ansari 2014[27]	Abstract
Ardic 2002[29]	Not guideline condition. Incorrect population
Aridici 2016[30]	Incorrect interventions. Inappropriate comparison
Attal 2010[32]	Abstract
Avery 2015[33]	No useable outcomes
Ay 2011[34]	Incorrect population (not chronic)

Study	Exclusion reason
Azatcam 2017[35]	Incorrect population (myofascial pain, unclear duration)
Barbosa 2018[36]	Incorrect comparison
Barnhoorn 2015[38]	Incorrect interventions
Barr 1987[39]	Abstract
Barr 2004[40]	Crossover study
Bates 1980[41]	Incorrect study design: not randomised
Baudic 2013[42]	Incorrect outcome
Bergeron-vezina 2018[43]	Incorrect population
Bezuur 1988[44]	Incorrect population (not chronic pain)
Biemans 2013[45]	Incorrect population. Not primary pain
Bilgili 2016[46]	Combinations of interventions. Combined with water bath and exercise
Bingol 2005[47]	Incorrect population (not chronic pain)
Bjordal 2003[48]	Incorrect study design
Boggio 2009[49]	Crossover study
Borckardt 2011[50]	Incorrect population. Healthy population
Botelho 2018 [51]	Unclear intervention duration
Boureau 1981[52]	Incorrect interventions
Busch 2013[55]	Incorrect population. Healthy population
Canadian chiropractic 2005[57]	Incorrect study design: expert opinion/guideline
Carbonario 2013[58]	Combinations of interventions. Intervention combined with exercise
Carrasco 2008[60]	Incorrect population (not chronic pain)
Carrasco 2009[59]	Incorrect population (not chronic pain)
Castro-sanchez 2011[63]	Incorrect interventions. Inappropriate comparison. Combinations of interventions
Castro-sanchez 2020 [62]	Inappropriate comparison
Ceccherelli 1989[64]	Not guideline condition. Not primary pain
Cervigni 2018[65]	Crossover study
Cetiner 2006[66]	Incorrect population (not chronic pain)
Chabal 1998[67]	Incorrect study design (survey)
Chan 2009[68]	Incorrect interventions. Acupuncture
Chee 1986[69]	Incorrect population (not chronic pain)
Chen 2008[70]	Incorrect population. Not primary pain
Cheng 1986[72]	Incorrect interventions. Acupuncture
Cheng 2019 [71]	No useable outcomes (correlational GLM model)
Choi 2014[74]	Incorrect population. Not chronic pain
Choi 2018[73]	Incorrect population. Not primary pain
Chong 2018[75]	Incorrect interventions. Electric acupuncture
Chow 2005[76]	Incorrect population (not chronic pain)
Cohen 2012[79]	Incorrect population. Incorrect interventions. Acupuncture
Conti 1997[80]	No useable outcomes
Conti 2014[81]	No useable outcomes
Cormier 2013[82]	Incorrect population.
Correa 2016[83]	Incorrect population.
Cossins 2013[84]	Systematic review is not relevant to review question or unclear PICO

Study	Exclusion reason
Costa 2017[85]	Incorrect study design (1 day study)
Cruccu 2016[86]	Incorrect study design: expert opinion.
Cruccu 2016[87]	Incorrect study design. Systematic review is not relevant to review question or unclear PICO
Cruz 2018[88]	Incorrect population
Cummiford 2016[89]	Crossover study
Curatolo 2017[90]	No useable outcomes
Dailey 2013[93]	Crossover study
De carli 2013[97]	Incorrect population. Combinations of interventions
De giorgi 2017[98]	No useable outcomes
De souza 2018[99]	Inappropriate comparison
Defrin 2005[100]	Incorrect population. Not primary pain
Deluze 1992[102]	Incorrect interventions. Electric acupuncture
Demirkol 2015[103]	Incorrect population. Not chronic pain.
Desantana 2017[104]	Conference abstract
Di benedetto 1993[105]	Inappropriate comparison
Dibai-filho 2017[106]	Combinations of interventions
Dimitrijevic 2014[107]	Incorrect population. Not chronic pain.
Dorsher 2010[108]	Incorrect interventions. Electrical acupuncture
Dundar 2007[109]	Incorrect population. Not chronic pain.
Dundar 2014[110]	Abstract
Dundar 2015[111]	Combinations of interventions. Intervention combined with exercise
Durmus 2013[112]	Incorrect population
Eken 2018[113]	No relevant outcomes
El-Gendy 2019 [114]	Incorrect intervention. Combination of electrotherapies
Emshoff 2008[115]	Incorrect population. Not chronic pain
Escortell-mayor 2011[116]	Inappropriate comparison
Euasobhon 2018[118]	Incorrect population. Neuropathic pain
Falaki 2014[121]	Incorrect population. Not primary pain
Fernandez-rodriguez 2018[122]	Incorrect interventions. Acupuncture
Ferreira 2013[123]	Incorrect interventions. Acupuncture
Field 1992[124]	Abstract
Fikackova 2007[125]	Incorrect population. Not chronic pain
Foletti 2018[126]	Incorrect population. Not primary pain
Franco 2018[127]	Systematic review is not relevant to review question or unclear PICO
Frank 2013[128]	Incorrect population. Neuropathic pain
Fricova 2013[130]	Incorrect interventions. Not primary pain
Galhardoni 2015[131]	Systematic review is not relevant to review question or unclear PICO
Gam 1993[132]	Systematic review is not relevant to review question or unclear PICO
Gemmell 2011[133]	No relevant outcomes
Gendreau 2014[134]	Abstract
Germano maciel 2018[135]	Combinations of interventions. Intervention combined with exercise
Gibson 2017[136]	Incorrect population. Neuropathic pain

Study	Exclusion reason
Goudra 2017[138]	Systematic review is not relevant to review question or unclear PICO
Graff-radford 1989[139]	Incorrect population (myofascial pain, unclear duration)
Graham 2013[140]	Systematic review is not relevant to review question or unclear PICO
Gray 1994[141]	Incorrect population. Not chronic pain
Gross 2000[142]	Systematic review is not relevant to review question or unclear PICO
Gross 2013[143]	Incorrect population. Systematic review is not relevant to review question or unclear PICO
Guedj 2013[144]	Conference abstract
Guirro 2015[145]	No useable outcomes
Guo 2005[146]	Incorrect interventions. Acupuncture
Gur 2002[148]	No useable outcomes (not validated scales)
Gur 2013[149]	Incorrect interventions. Inappropriate comparison
Hakguder 2003[150]	Incorrect population. Not chronic pain
Hargrove 2012[151]	No relevant outcomes
Harvey 2017[152]	Incorrect population. Over 20% of the population have chronic low back pain
He 2017[153]	Combinations of interventions
Hong 1993[154]	Crossover study
Hou 2002[155]	Incorrect population. Not chronic pain
Hou 2016[156]	Combinations of interventions. Incorrect study design
Hruby 2006[157]	Incorrect study design (cystoscopy)
Hsu 2018[158]	Incorrect study design: expert opinion
Hsueh 1997[159]	Incorrect population. Not chronic pain
Hurt 2020 [160]	Incorrect intervention. Extracorporeal shockwave therapy
Ilbuldu 2004[161]	Incorrect interventions. Acupuncture
Ilter 2014[162]	Combinations of interventions. Incorrect population. Not chronic pain
Ilter 2015[163]	Incorrect population. Not chronic pain
Istek 2014[164]	Incorrect population. Not primary pain
Ito 2002[165]	No relevant outcomes
Ivanishvili 2017[166]	Incorrect population. Neuropathic pain
Janice jimenez-torres 2017[168]	Protocol
Jeans 1979[169]	Incorrect population. Not primary pain
Jeon 2012[170]	Incorrect interventions. Combinations of interventions
Jin 2015[171]	Incorrect population. Neuropathic pain
Johansson 1980[172]	Incorrect study design
Johnson 2007[173]	Systematic review is not relevant to review question or unclear PICO
Johnson 2016[175]	Protocol
Johnson 2017[174]	Cochrane review is not relevant to review question or unclear PICO
Kadhim-saleh 2013[177]	Incorrect population. Not chronic pain
Kara 2010[178]	Incorrect population. Not primary pain
Kato 2006[179]	No useable outcomes
Katsoulis 2010[180]	Incorrect interventions. Acupuncture

Study	Exclusion reason
Kavadar 2015[181]	Incorrect population. Not chronic pain
Kavvadias 2012[182]	Incorrect study design: expert opinion
Kemler 2001[183]	Incorrect interventions. Spinal cord stimulation
Kessler 2014[184]	Incorrect interventions. No relevant outcomes
Kim 2014[186]	Incorrect population (latent trigger points)
Kiraly 2018 [187]	Incorrect comparison
Knijnik 2016[188]	Systematic review is not relevant to review question or unclear PICO
Koca 2014[189]	Incorrect interventions. Inappropriate comparison
Kohutova 2017[190]	Incorrect interventions
Kriek 2015[191]	Crossover study
Kroeling 2005[193]	Incorrect population. Not chronic pain.
Kroeling 2013[192]	Systematic review is not relevant to review question or unclear PICO
Kruger 1998[194]	Incorrect study design
Kulekcioglu 2003[195]	Not guideline condition. Not chronic pain
La bianca 2017[196]	Conference abstract
Laakso 1997[197]	No useable outcomes
Lagueux 2018[198]	Combinations of interventions
Langley 1984[199]	Crossover study
Lara-palomo 2013[200]	Incorrect population.
Lassemi 2008[201]	Not guideline condition. Not chronic pain
Lauretti 2013[202]	All participants allocated to amitriptyline 25-50mg per day at least 3 weeks before randomisation
Leandri 1990[203]	Incorrect population
Lee 1997[204]	No useable outcomes
Lee 2013[206]	Abstract
Lev-sagie 2017[207]	Incorrect population
Lewis 2013[208]	Incorrect population. Not chronic pain
Lewis 2018[209]	Incorrect population. Neuropathic pain
Lichtbroun 2001[210]	No useable outcomes
Lima 2008[211]	Systematic review is not relevant to review question or unclear PICO
Lindholm 2015[212]	Crossover study
Lopez-martos 2018[213]	Incorrect interventions. Acupuncture
Luan 2019 [214]	Incorrect intervention. Extracorporeal shockwave therapy
Luedtke 2012[215]	Incorrect population
Lyskov 2005[216]	Crossover study
Macdonald 1995[217]	Not randomised
Macpherson 2017[218]	Incorrect interventions. Electric acupuncture
Madani 2020 [219]	No useable outcomes
Maestu 2013[220]	No useable outcomes
Magri 2017[221]	No useable outcomes
Magri 2018[222]	No useable outcomes
Maia 2012[223]	Incorrect study design. Systematic review is not relevant to review question or unclear PICO

Study	Exclusion reason
Majithia 2016[224]	Systematic review is not relevant to review question or unclear PICO
Majlesi 2004[225]	Not chronic pain
Maloney 2014[226]	Conference abstract
Manafnezhad 2019 [227]	Incorrect interventions
Manca 2014[228]	Not chronic pain
Manfredini 2017[229]	Inappropriate comparison. No placebo
Marchand 1991[230]	Incorrect population
Marineo 2012[231]	Incorrect interventions. Inappropriate comparison
Marini 2010[232]	Incorrect population (disc displacement)
Marlow 2013[233]	Systematic review is not relevant to review question or unclear PICO
Matsutani 2007[234]	Incorrect interventions
Mazzetto 2007[235]	Not chronic pain. Incorrect population
Medeiros 2016[236]	Combinations of interventions. rTMS combined with sham DIMST (needling)
Mekhail 2018[237]	Conference abstract
Melchior 2013[238]	Not chronic pain. Incorrect population
Mendonca 2011[239]	No useable outcomes
Mendonca 2016[240]	Combinations of interventions. Intervention combined with exercise
Moisset 2016[242]	Incorrect study design: expert opinion
Molina-torres 2016[243]	Incorrect population.
Mordasini 2014[244]	Conference abstract
Moretti 2012[245]	Combinations of interventions. Inappropriate comparison
Morin 2017[246]	Incorrect population. Episodic pain
Müller 2015[247]	Incorrect interventions. Acupuncture
Munguia 2018[248]	Systematic review is not relevant to review question or unclear PICO
Muniswamy 2016[249]	Incorrect population. Neuropathic pain
Murina 2018[251]	Combinations of interventions
Mutlu 2006[253]	Unavailable
Mutlu 2013[252]	Not guideline condition. Not chronic pain
Mysliwiec 2012[254]	Incorrect population. Not primary pain
Nadershah 2020 [255]	Unclear population. Unclear duration of pain
Nardone 2018[256]	Systematic review is not relevant to review question or unclear PICO
Naterstad 2015[257]	Incorrect population.
Nct 2009[260]	Unpublished
Niddam 2007[262]	Not randomised
Noehren 2015[263]	Abstract
Nordin 1999[264]	Incorrect study design: review of guidelines
O'connell 2011[267]	Duplicate results
O'connell 2013[265]	Incorrect population.
O'connell 2018[266]	Systematic review is not relevant to review question or unclear PICO
Ofluoglu 2013[268]	Non-English language studies
Okmen 2017[269]	Incorrect population. Chronic Not primary pain

Study	Exclusion reason
Oosterhof 2006[270]	Incorrect population
Oosterhof 2008[271]	Incorrect population (neuropathic pain, osteoarthritis)
Oosterhof 2012[272]	No useable outcomes
Oosterhof 2012[273]	Incorrect population. Not primary pain
Park 2018 [275]	Incorrect comparison (high versus low intensity)
Passard 2007[276]	No useable outcomes
Peng 1987[277]	Incorrect interventions. Electric acupuncture
Perrot 2014[278]	Systematic review is not relevant to review question or unclear PICO
Pezelj-ribaric 2013[279]	Incorrect population. Not chronic pain
Picarelli 2010[281]	Combinations of interventions. Combined with pharmacological therapy
Picarelli 2012[280]	Abstract
Plazier 2014[282]	Incorrect interventions
Powers 2018[283]	Combinations of interventions
Rayegani 2011[284]	Incorrect interventions
Reid 2001[285]	Case study
Renzenbrink 2004[286]	Incorrect population. Not primary pain
Riberto 2011[287]	Combinations of interventions. Intervention combined with exercise
Rigby 2017[288]	Incorrect population. Not chronic pain
Roizenblatt 2007[290]	No useable outcomes
Rollnik 2002[291]	Incorrect population. Not primary pain
Rowe 2005[292]	No useable outcomes
Ruiz-lopez 2017[293]	Non-English language studies
Ryan 2017[294]	Incorrect intervention (combined with a range of therapy from a physiotherapist, including but not limited to: CBT, hydrotherapy, motor imagery)
Sahin 2010[296]	No abstract/results
Sahin 2011[295]	Incorrect population (myofascial pain, duration unclear)
Sakrajai 2014[297]	Combinations of interventions. Incorrect population. Not chronic pain
Salazar 2017[298]	Combinations of interventions
Saltychev 2017[299]	Systematic review is not relevant to review question or unclear PICO
Sancakli 2015 [301]	Unclear population (no minimum duration of pain)
Santos 2018 [302]	No relevant outcomes
Sator-katzenschlager 2003[304]	Incorrect population. Incorrect interventions. Electric acupuncture.
Sator-katzenschlager 2004[303]	Incorrect interventions. Incorrect population. Electric acupuncture.
Sattayut 2012[305]	Crossover study
Sayilir 2017[307]	Incorrect population.
Sayilir 2018 [306]	Incorrect intervention (combination electrotherapy)
Schabrun 2012[308]	Incorrect population. Not chronic pain
Shafik 2006[309]	Incorrect population. Not primary pain
Shimoji 2007[310]	Incorrect population. Not primary pain
Shirani 2009[311]	Incorrect population. Not chronic pain
Shobha 2017[312]	No useable outcomes
Short 2010[313]	Abstract

Study	Exclusion reason
Silva 2017[315]	Crossover study
Simons 2006[316]	Incorrect interventions. Inappropriate comparison
Simpson 2009[317]	Unpublished
Skorupska 2012[318]	Incorrect population. Not primary pain
Skrinjar 2020 [319]	No useable outcomes
Slattery 2002[320]	Conference abstract. Unavailable
Smania 2003[321]	Incorrect population. Not primary pain
Smania 2005[322]	No useable outcomes
Snyder-mackler 1986[323]	Incorrect population. Not primary pain
Soysal 2013[324]	Combinations of interventions
Spanemberg 2019 [326]	No useable outcomes
Srbely 2007[327]	Incorrect population. Not chronic pain
Stonnington 1976[328]	Incorrect study design. Not randomised
Sunshine 1996[330]	No useable outcomes (no variability data)
Sutton 1997[331]	Endometriosis. Incorrect population
Takla 2018 [333]	Incorrect population (not chronic primary pain)
Takla 2018 [332]	No useable outcomes
Tanwar 2016[334]	Conference abstract
Taube s 1988[335]	Incorrect outcome. No useable outcomes
Taylor 1987[337]	Incorrect population (not chronic pain)
Taylor 2004[338]	Incorrect outcome. Cost-effectiveness study
Taylor 2013[336]	Incorrect interventions
Thorsteinsson 1977[340]	Incorrect population
Tieppo francio 2017[341]	Not primary pain. Osteoarthritis
Tirlapur 2013[342]	Systematic review is not relevant to review question or unclear PICO. Incorrect study design
To 2017[343]	No useable outcomes
Uemoto 2013[344]	Incorrect study design. No useable outcomes
Valle 2009[347]	No results
Van der windt 1999[348]	Systematic review is not relevant to review question or unclear PICO
Vance 2015[349]	Incorrect study design. Not randomised
Vas 2006[350]	Incorrect interventions. Acupuncture
Vaseghi 2014[351]	Systematic review is not relevant to review question or unclear PICO
Vaseghi 2015[352]	Systematic review is not relevant to review question or unclear PICO. Systematic review: study designs inappropriate
Vayvay 2016[353]	Intervention combined with exercise. Combinations of interventions
Venezian 2010[355]	Not guideline condition. Not chronic pain
Viana 2012[356]	Not primary pain. Stroke patients
Visnjevac 2017[357]	Incorrect interventions. Systematic review is not relevant to review question or unclear PICO
Vitiello 2007[358]	Incorrect population
Vrijens 2017[359]	Systematic review is not relevant to review question or unclear PICO
Vukoja 2011[360]	Incorrect study design. Letter to editor
Walker 1987[361]	Incorrect population. Neuropathic pain

Study	Exclusion reason
Wang 2011[363]	Non-English language studies
Wang 2014[362]	Incorrect population. Perioperative. Incorrect interventions. Acupuncture
Wang 2014[364]	Incorrect population. Not chronic pain
Waschl 2014[365]	Unavailable
Weisstanner 2014[367]	No relevant outcomes
Weisstanner 2017[368]	No relevant outcomes
Weng 2005[369]	Incorrect interventions
White 2000[372]	Crossover study
White 2007[370]	Incorrect interventions. Acupuncture
White 2012[371]	Incorrect interventions. Acupuncture
Wiffen 2005[373]	Incorrect population. Palliative care
Wilson 2014[374]	No useable outcomes
Yang 2018 [376]	Not in English
Yatci 2013[377]	Incorrect study design: expert opinion
Yesil 2017[378]	Incorrect interventions. Combinations of interventions
Yesil 2018[379]	Unavailable
Yildirim 2018 [380]	Incorrect population (pain for less than 6 weeks)
Yoshimizu 2012[381]	Crossover study
Young 1987[382]	Incorrect study design. Not randomised
Yuksel 2019 [383]	Incorrect comparison (healthy controls)
Zhu 2002[385]	Incorrect interventions. Acupuncture
Zhu 2017[384]	Systematic review is not relevant to review question or unclear PICO

I.2 Excluded health economic studies

None.

Appendix J: Research recommendations

J.1 Laser therapy

Research question: What is the clinical and cost-effectiveness of laser therapy for managing chronic primary pain in people aged 16 years and over?

Why this is important:

Laser therapy involves the non-invasive application of a single wavelength of light to the skin over the painful area using a probe. There are various laser devices and probe configurations in clinical use. The light is absorbed in the tissues and it is hypothesised that this results in local heating and effects on local chemical activity and cellular behaviour. It is through those effects that laser therapy is purported to have an anti-inflammatory effect and promote tissue repair.

14 studies were included in this review comparing laser to sham in a range of conditions including burning mouth syndrome (4 studies), temporomandibular pain (4 studies), fibromyalgia (3 studies), neck pain (2 studies) and myofascial pain (1).

While evidence of clinical benefit was observed there remains uncertainty regarding the efficacy and effectiveness of laser therapy, though there is some promising evidence. There is therefore a need for high quality trials into the effectiveness and cost effectiveness of laser therapy for chronic primary pain.

Criteria for selecting high-priority research recommendations:

PICO question	Population: Adults (aged >16) with Chronic Primary Pain Intervention(s): Laser therapy Comparison: Sham Outcome(s): Quality of life, Pain Interference and reduction,
Importance to patients or the population	If laser therapy offers clinically important benefits over sham laser therapy when added to care, at a reasonable cost threshold then it may be an important modality to enhance clinical outcome in this patient group.
Relevance to NICE guidance	This research will reduce the existing uncertainty regarding the effectiveness and cost-effectiveness of laser therapy and enable future guidelines to clearly recommend for or against the use of laser therapy.
Relevance to the NHS	A clear recommendation for or against laser therapy will offer clinicians clearer guidance on best care for chronic primary pain.
National priorities	None
Current evidence base	The NICE chronic pain guideline found very low to moderate quality evidence for improvement with laser therapy in quality of life in the short term and one small study showing a clinically important benefit in QOL in the long term. Although there was evidence from thirteen studies demonstrating a clinically important benefit in pain reduction in the short term, this was rated as very low quality evidence. Two further studies demonstrated clinically important benefit in pain reduction in the longer term (moderate quality evidence). However no clinically important difference was noted for psychological distress or discontinuation. Conflicting evidence was found comparing laser with sham for pain and quality of life outcomes. While evidence of clinical benefit was observed in some comparisons for pain and quality of life, there were concerns with the quality and applicability of the evidence. There remains uncertainty regarding the efficacy and effectiveness of laser therapy, though there is some promising evidence. No cost-effectiveness evidence has been identified regarding use of laser for the management of chronic primary pain. However the NICE chronic pain guideline committee noted that there

	would be resource implications, including the provision and maintenance of equipment and training therapists. There is therefore a need for a conclusive study into the clinical and cost effectiveness of laser therapy for chronic primary pain.
Equality	The recommendation is unlikely to impact on equality issues.
Study design	Randomised controlled trial with corresponding economic analysis. Post-intervention long term follow up should be included.
Feasibility	The trial is feasible and should be straightforward to carry out. There are challenges associated with the design of adequate sham controls for higher intensity laser therapy that delivers a sensation of heating that will require specific consideration when designing a trial.
Other comments	Low intensity laser therapy is easy to design sham controls for since it delivers no sensation beyond the pressure of the probe. A recommendation for laser therapy is likely to require the purchase of new equipment and staff training.
Importance	Low: the research is of interest and will fill existing evidence gaps.

J.2 Transcranial magnetic stimulation

Research question: What is the clinical and cost effectiveness of transcranial magnetic stimulation for managing chronic primary pain in people aged 16 years and over?

Why this is important:

Transcranial magnetic stimulation (TMS) has been proposed as a potential treatment option for chronic pain as stimulation of the motor cortex of the brain is known to lead to analgesia. TMS has been researched in various chronic pain conditions including those that fall within the definition of chronic primary pain. However, whether or not TMS is an effective and cost-effective treatment option for chronic primary pain remains unclear. TMS is not provided as part of current clinical practice for people with chronic primary pain and its introduction into practice would incur costs in terms of provision of the equipment and training in the use of the equipment, and therefore good quality research is required to inform this decision.

Criteria for selecting high-priority research recommendations:

PICO question	Population: Adults (aged >16) with chronic primary pain Intervention(s): TMS Comparison: Sham TMS or usual care Outcome(s): Pain reduction, health related quality of life, physical function, psychological distress, pain interference, pain self-efficacy.
Importance to patients or the population	There was a suggestion from the current evidence base that TMS may help improve pain in people with chronic primary pain. Further evidence to determine whether this benefit can be replicated in larger trials, or also has an impact on quality of life would help inform whether this should be a treatment choice for this population.
Relevance to NICE guidance	More evidence from a large RCT would help inform an update of this guideline to guide a recommendation on whether TMS should or should not be recommended for people with chronic primary pain.
Relevance to the NHS	TMS is not routinely used in current NHS practice to treat chronic primary pain, therefore good high quality evidence would be of relevance to inform whether a change in practice is warranted.
National priorities	N/A
Current evidence base	Eight studies of TMS in people with chronic primary pain were included in the guideline review. When compared to sham there was some indication of benefit in quality of life and pain interference, however this evidence was inconsistent and from relatively small sample sizes. There was more

	evidence for a reduction in pain intensity, but in the absence of consistent benefit in other outcomes, or long term benefit, this was considered insufficient to base a recommendation on.
Equality	No specific equality issues.
Study design	An adequately powered, sham controlled, RCT with a follow-up period of greater than 3 months.
Feasibility	The design of this research is feasible, although it is noted that TMS is not widely available, which may have an impact.
Other comments	None.
Importance	Low: the research is of interest and will fill existing evidence gaps.

Appendices

Appendix K: MIDs for continuous outcomes

Table 24: MIDs for continuous outcomes: Laser therapy versus sham laser therapy

Outcomes	MID
Quality of life at ≤3 months (Oral health impact profile, FIQ, high is poor outcome, final values)	0.5 (SMD)
Quality of life at >3 months (Oral health impact profile, FIQ, high is poor outcome, final values)	0.5 (SMD)
Pain reduction at ≤3 months (VAS, NRS, FIQ pain scale, high is poor outcome, 0-10, final values and change scores)	0.79
Pain reduction at >3 months (VAS, high is poor outcome, 0-10, final values)	0.6
Psychological distress at ≤3 months (Hospital anxiety and depression rating scale, anxiety subscale, 0-21, high is poor outcome, final values)	1.75
Psychological distress at ≤3 months (Hospital anxiety and depression rating scale, depression subscale, 0-21, high is poor outcome, final values)	2.25

Table 25: MIDs for continuous outcomes: TMS versus sham TMS

Outcomes	MID
Quality of life at ≤3 months (WHOQOL-BREF physical domain, 4-20, high is good outcome, final values)	1.42
Quality of life at ≤3 months (WHOQOL-BREF psychological domain, 4-20, high is good outcome, final values)	1.245
Quality of life at ≤3 months (FIQ, 0-100, high is poor outcome, final values)	8.395
Quality of life at >3 months (FIQ, 0-100, high is poor outcome, final values)	7.5
Pain reduction at ≤3 months (VAS, McGill Pain questionnaire, 0-10, high is poor outcome, final values)	1.05
Physical function at ≤3 months (BPI functional impairment subscale, 0-10, high is poor outcome, final values)	1.345
Psychological distress at ≤3 months (Beck depression inventory, 0-61, high is poor outcome, final values and change scores)	2.55
Psychological distress at ≤3 months (Hamilton depression rating scale, MADRS, BDI, high is poor outcome, final values)	0.5 (SMD)
Psychological distress at ≤3 months (HADS anxiety, 0-21, high is poor outcome, change scores)	1.15
Psychological distress at >3 months (HADS anxiety, 0-21, high is poor outcome, change scores)	2.85
Psychological distress at >3 months (HADS depression, 0-21, high is poor outcome, change scores)	2

Outcomes	MID
Pain interference at >3 months (BPI pain interference, 0-10, high is poor outcome, final values)	0.75

Table 26: MIDs for continuous outcomes: TDCS versus sham TDCS

Outcomes	MID
Pain reduction at ≤3 months (NRS, VAS, 0-10, high is poor outcome, final values)	0.75
Psychological distress at ≤3 months (Hospital anxiety and depression scale, HAM-A, anxiety subscales, high is poor outcome, final values)	0.5 (SMD)
Psychological distress at ≤3 months (Hospital anxiety and depression scale, BDI, HAM-D, depression subscales, high is poor outcome, final values)	0.5 (SMD)
Sleep at ≤3 months (PSQI, scale range not reported, high is poor outcome, final values)	1.87

Table 27: MIDs for continuous outcomes: TENS versus sham TENS

Outcomes	MID
Quality of life at ≤3 months (SF36 physical T scores, high is good outcome, change scores)	3.15
Quality of life at ≤3 months (SF36 mental T scores, high is good outcome, change scores)	5.05
Pain reduction at ≤3 months (BPI intensity, VAS, 0-10, high is poor outcome, final values and change scores)	0.94
Physical function at ≤3 months (6 minute walk test, change scores)	157
Psychological distress at ≤3 months (PROMIS depression T scores, high is poor outcome, change scores)	4.15
Psychological distress at ≤3 months (PROMIS anxiety T scores, high is poor outcome, change scores)	4.18
Pain interference at ≤3 months (BPI interference, 0-10, high is poor outcome, change scores)	1.09
Pain self-efficacy at ≤3 months (PSEQ, 0-60, high is good outcome, change scores)	6.6

Table 28: MIDs for continuous outcomes: TENS versus usual care

Outcomes	MID
Quality of life at ≤3 months (SF36 physical T scores, high is good outcome, change scores)	3.25
Quality of life at ≤3 months (SF36 mental T scores, high is good outcome, change scores)	5.15
Pain reduction at ≤3 months (BPI intensity, 0-10, high is poor outcome, change scores)	0.91
Physical function at ≤3 months (6 minute walk test, change scores)	160.25

Outcomes	MID
Psychological distress at ≤3 months (PROMIS depression T scores, high is poor outcome, change scores)	4.05
Psychological distress at ≤3 months (PROMIS anxiety T scores, high is poor outcome, change scores)	4.13
Pain interference at ≤3 months (BPI interference, 0-10, high is poor outcome, change scores)	1.27
Pain self-efficacy at ≤3 months (PSEQ, 0-60, high is good outcome, change scores)	6.63

Table 29: MIDs for continuous outcomes: PENS versus sham PENS

Outcomes	MID
Quality of life at ≤3 months (NIH-CPSI, 0-12, high is poor outcome, final values)	1.05
Pain reduction at ≤3 months (VAS, 0-10, high is poor outcome, final values)	0.2

Table 30: MIDs for continuous outcomes: PENS versus usual care

Outcomes	MID
Pain reduction at ≤3 months (VAS, 0-10, high is poor outcome, final values)	0.44

Table 31: MIDs for continuous outcomes: Therapeutic ultrasound versus usual care

Outcomes	MID
Pain reduction at ≤3 months (VAS, 0-10, high is poor outcome, final values)	0.44