National Institute for Health and Care Excellence

Draft

Multiple sclerosis in adults: management (update)

[G] Evidence reviews for non-pharmacological management of pain

NICE guideline <number>

Evidence reviews underpinning recommendations 1.5.33 to 1.5.36 and research recommendations in the NICE guideline

December 2021

Draft for Consultation

These evidence reviews were developed by National Guideline Centre, hosted by Royal College of Physicians

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1 Non-pharmacological management of pain in MS

1.1 Review question

For adults with MS, including people receiving palliative care, what is the clinical and cost effectiveness of non-pharmacological interventions for pain?

1.1.1 Introduction

NICE have developed a clinical guideline on the pharmacological management of neuropathic pain, and this has included people with MS. Due to the limited pharmacological response and significant side effects caused by medication used for the treatment of neuropathic pain there is still a huge need for further treatment. The guideline scope included non-pharmacological management of pain in people with MS. The aim of this review to identify clinical and cost-effective treatments interventions.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Inclusion: Adults (≥18 years) with MS, including people receiving palliative care. Studies with mixed populations for example MS patients and spinal cord injury patients may be considered if they include at least 60% people with MS.
Interventions	Any non-pharmacological intervention, for example: • Multidisciplinary rehabilitation programmes • Acupuncture • Self-management programmes • Exercise (for example stretching, standing, splinting, gym prescription, yoga, tai chi, pilates, relaxation) • Lycra garments • Transcutaneous electrical nerve stimulation (TENS) • Psychological based therapies: CBT, hypnosis, • Mindfulness • Hydrotherapy • Complementary therapies (e.g., massage) • TMS (transcranial magnetic stimulation)
Comparisons	Interventions will be compared to each other, placebo, sham, no treatment or usual care.
Outcomes	• Pain intensity using validated pain scales for example Visual Analogue Scale (VAS) and Numerical Rating Scale (NRS) • Pain reduction for example >30% and 50% pain reduction from baseline • Patient-reported outcome measures, which refer generally to quality of life and the scales of Multiple Sclerosis Quality of Life Inventory (MSQLI); life satisfaction, EQ5D, SF-36

	• Adverse effects of treatment. • Adverse events leading to withdrawal or lack of efficacy • Expanded Disability Status Scale (EDSS) • MS Functional Composite or its subscales if not reported (MSFC). • Functional improvement • Reduction of care • Mood related outcomes for example validated depression scales and anxiety scales • Changes in sleep quality/sleep related impairments/ sleep disturbance Follow up: • 3 months up to 6 months (less months may be included in view of palliative care subgroup) • If studies only report > 6 months, these may be included and downgraded for indirectness.
Study design	Systematic reviews of RCTs and RCTs will be considered for inclusion. Cross-over trials will also be considered for inclusion If there insufficient RCT evidence, non-randomised cohort studies will be considered provided they have adjusted for the following variables: - age - fatigue - depression - anxiety - gender

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

Twenty four studies (25 papers) were included in the review[1, 2, 4-7, 11-16, 18-23, 26, 27, 32-34, 36, 37]; these are summarised in Table 2 below.

Six of these studies were included in the previous guideline[1, 7, 19, 22, 23, 34] and the remainder were new studies retrieved from the update search. The majority of the studies were parallel randomised controlled trails except for 2 which were randomised cross over trials and one mixed methods (qualitative and quantitative).

Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

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

Due to the limited number of randomised trials for each intervention, the search was extended to non-randomised studies to look for further trials that may support or strengthen the evidence. However, no non-randomised controlled trials relevant to the protocol were identified.

Population:

The population for this review question was broadened to potentially include studies with mixed populations, for example including spinal cord injury patients where >60% of participants were MS patients. This was to account for the fact that in the last decade pain research has shifted from an aetiology-based approach to classification by type of pain and there may be recent studies that may be in mixed populations and not be exclusively in people with MS.

All the included studies in this review were in patients with MS and no studies with mixed population were found. Many studies included younger patients with a mean age across the studies ranging from 30 to 50 years old. Where studies reported the proportions of participants with different types of MS, relapsing-remitting MS was the most common type of MS among participants.

The range of Expanded Disability Status Scale (EDSS) scores included in studies was generally low and less than 6 (less disability). In many studies, particularly where the intervention required a certain level of activity, EDSS score was used as an inclusion criterion.

The type of pain was not always reported in studies. Where it is was reported, participants had experienced pain that included chronic pain, neuropathic pain or musculoskeletal pain in the lower back, legs, feet, shoulders, hips arms or eyes. Pain intensity rather than pain type was more commonly used as an inclusion criterion. A large proportion of participants had at least moderate pain (>3-4 on a visual analogue scale) at baseline.

Participants with mood disorders or psychiatric conditions were often excluded from studies particularly where interventions included psychological therapy.

There were no identified studies that were specific to or included palliative care patients.

Interventions and comparisons covered by the evidence:

Evidence was identified for the following interventions and comparisons:

- Yoga
- Exercise – resistance training
- Exercise including progressive resistance training, strength, aerobic and balance
- Massage
- Reflexology
- Relaxation including progressive muscle relaxation
- Psychological based therapies including mindfulness meditation, cognitive behavioural therapy (CBT), self-hypnosis training and self-management programmes.
- Hydrotherapy (Ai Chi)
- Neuromodulation including transcranial Direct Current Stimulation (tDCS), transcranial Random Noise Stimulation (tRNS) and transcutaneous spinal Direct Current Stimulation (tsDCS)
- Transcutaneous electrical nerve stimulation (TENS)

There was no evidence for multidisciplinary rehabilitation programmes, lycra garments, acupuncture or transcranial magnetic stimulation.

There was a wide range of interventions and comparisons across the studies and outcomes were reported in various ways both within and across studies. Many interventions were used in specific programmes or contexts and were therefore not directly comparable.

No studies reported percentage reduction in pain for example >30% or >50% reduction in pain from baseline

Studies from the previous guideline

All studies from the previous guideline were included. However, these could not be meta-analysed as some only reported median IQR or were single studies reporting specific interventions. Warke 2004[35] has been updated to Warke 2006[34] which is an extension of the original study.

Meta-analysis

Pooling of the data was not possible in most cases due to different interventions used in specific programs or context, different comparators and different outcomes reported. For example, a meta-analysis of the data from 2 studies, one on relaxation and one on progressive muscle relaxation compared to control was attempted but I^2 was equal 98% indicating very significant heterogeneity and therefore these studies were analysed separately. This wide variety in the included studies resulted in many different comparisons presented and outcome data from single small studies. Where possible, studies using the same intervention, but outcomes measured on different scales, the data was pooled and analysed using the standardised mean difference method.

Some studies only reported medians and interquartile ranges (IQR). These were included in the review but could not be entered into Review Manager or analysed using GRADE. These studies were either summarised narratively or in separate tables.

1.1.4.2 Excluded studies

One Cochrane review[3] was identified but was not included because it was specific to patients experiencing chronic pain and our review question is much broader and does not specify the type of pain as an inclusion criterion. Therefore, it would not have captured all the relevant studies for this review. In addition, all risk of bias assessments were done on individual studies rather than by outcome as required for our methods.

See the excluded studies list in Appendix J

1.1.5 Summary of studies included in the effectiveness evidence

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Relevant outcomes	Comments
Al-Smadi 2003[1] RCT N=15 Conducted in the USA	TENS – two different groups of different frequencies N=5 per group TENS group 1 consisted of low-frequency TENS (4 Hz, 200 µs) and group 2 consisted of high-frequency TENS (110 Hz, 200 µs). Both groups had TENS applied by a researcher for 45 min three times weekly for 6 weeks. Placebo TENS Applied three times weekly for 6 weeks, 45 min per session. Inactive TENS unit used in the placebo group.	Multiple sclerosis Pain type: musculoskeletal (low back pain in the lumbar spine for at least 3 months) Age: mean (SD) not reported, overall age was 34-65 years MS Type: not reported EDSS: not reported	Pain VAS – low back pain Right/left leg pain McGill Pain Questionnaire SF-36 physical and mental health component scores Leeds MS Quality of Life Questionnaire Roland Morris Disability Questionnaire	Authors present results incompletely meaning they could not be analysed and have therefore been summarised narratively in this review
Alschuler 2021[2] RCT N=27 Conducted in the USA	Psychological pain management intervention n=15 A single 120 min group videoconference session delivered via Zoom, focused on developing an adaptive set of pain coping strategies based upon cognitive–behavioural theories of pain. It included education on pain in MS and theoretical models of chronic pain and pain coping; relaxation training; a brief module on pacing; cognitive restructuring; and cognitive diffusion. This intervention was used as an adjunct to any existing treatments	Multiple sclerosis Pain type: not reported Mean age (SD): Intervention 40.14 (11.2); control 29.58 (12.3) MS Type(n): Intervention 13 relapsing remitting, 2 uncertain; Control 8 relapsing remitting, 2 uncertain, 2 not available or CIS	Pain interference (PROMIS) Pain catastrophising (PCS) Pain intensity (NRS 0-10) Depressive symptoms (PHQ-8)	Pilot/proof of concept study

Study	Intervention and comparison	Population	Relevant outcomes	Comments
	Usual Care n=12 Participants were instructed to continue with the care they would normally receive as part of their ongoing clinical care.	EDSS not reported		
Ayache 2016[4] Cross over RCT N=16 Conducted in France	Anodal transcranial Direct Current Stimulation (tDCS), n=8 A current was ramped up during the first 15 s to a maximum of 2 mA that was maintained throughout the 20-min stimulation session. Sham tDCS n=8 A current was ramped up during the first 15 s to a maximum of 2 mA then ramped down immediately after ramping up in order to achieve an effective blinding.	Multiple sclerosis Pain type: neuropathic Age: mean age 48.9 years, range 38-67 years Type of MS: relapsing remitting 11, secondary progressive 4, primary progressive 1	Pain VAS (0-100) HADS-Depression HADS-Anxiety	Wash out period was 3 weeks Note: Pain VAS outcome was favoured from the Ayache 2016 study as it could be pooled with another study. Other pain outcomes reported in the Ayache 2016 study were extracted but not analysed.
Berra 2019[5] RCT N=33 Conducted in Italy	Transcutaneous spinal DCS (ts-DCS) n=19 A 2 mA constant direct current for 20 min in each session with a density of 0.071 mA/cm2 and delivered a total charge of 63.9 mC/cm2. Sham n=14 Electrodes were placed in the same spots than real anodal stimulation, but the stimulator was programmed to automatically turn to 0 mA after 10 s.	MS patients Pain type: neuropathic ts-DCS group Mean age (SD) 57.6 (9.1) MS type: Relapsing remitting 1 (5.3%) 3 (21.4%), secondary progressive 14 (73.7%), primary progressive 4 (21.1%) EDSS score, mean (SD)5.9 (1.3)	Neuropathic Pain Symptoms Inventory (NPSI)	

Study	Intervention and comparison	Population	Relevant outcomes	Comments
		Sham group Mean age (SD) 54.0 (7.79) MS type: Relapsing remitting 3 (21.4%), secondary progressive 10 (71.4%), primary progressive 1 (7.1%) EDSS score, mean (SD) 5.9 (1.2)		
Bogosian 2015[6] RCT N=40 Conducted in the UK	Remotely delivered mindfulness intervention to relieve distress n=19 Eight one-hour long sessions delivered over 8 weeks via Skype video conference. Wait list n=21 Participants allocated to the waiting-list group received the treatment they would normally expect within the NHS.	Primary progressive and secondary progressive MS Pain type not reported Mean age (SD): Mindfulness 53.2 (8.3), waiting list 50.9 (9.9) Types of MS (n): primary progressive5, others not reported EDSS not reported	General Health questionnaire (GHQ-12) HADS-depression HADS-Anxiety MSIS-29 Pain intensity (NRS 0-10) EQ5D	
Castro-Sanchez 2012[7] RCT N=73 Conducted in Spain	Ai-Chi exercise n=36 A series of 16 movements performed in a warm water in a swimming pool and led by a physiotherapist. A combination of deep breathing and slow, broad movements of the	Multiple sclerosis Pain type: musculoskeletal pain (back, cervical, legs, feet, arms, shoulder)	Pain VAS MSIS-Physical MSIS-psychological	Included in previous guideline Reports medians and standard deviations and presented narratively

Study	Intervention and comparison	Population	Relevant outcomes	Comments
	arms, legs, and torso to work on balance, strength, relaxation, flexibility, and breathing. Control n=35 Abdominal breathing and Contraction-relaxation exercises in therapy room led by the same physiotherapist as the intervention group.	Ai-Chi Mean age (SD) 46 (9.97) EDSS (SD) 6.3 (0.8) MS type: primary progressive 6, secondary progressive 9, not known 21 Control Mean age (SD) 50 (12.31) EDSS (SD) 5.9 (0.9) MS type: primary progressive 9, secondary progressive: 12; not known 16.	Beck Depression Inventory II	
Doulatabad 2012[11] RCT N=60 Conducted in Iran	Yoga n=30 Pain-managing Yoga methods for three months, at the rate of eight 90-minute sessions per month. Control n=30 No Yoga (no further details reported)	Multiple sclerosis Mean Age (SD): 31.6 (8) Pain type, MS type and EDSS scores: not reported	MS QoL 54	
Dunne 2021[12] Mixed methods RCT N=55 Conducted in Australia	Mindfulness for Multiple Sclerosis (M4MS) n=18 A trained psychologist delivered a mindfulness meditation and mindful movement and psychoeducation during 8 weekly sessions via Zoom. Chair Yoga n=18 A registered yoga teacher delivered a	Multiple sclerosis Mean age (SD): 48.4 (10.9) Pain type, MS type and EDSS not reported	MS QoL 54 Brief Pain Inventory (BPI)	Data only presented as Median (IQR)

Study	Intervention and comparison	Population	Relevant outcomes	Comments
	program focussed on simple movements incorporating breathing and relaxation techniques adapted from traditional Hatha Yoga with movements conducted while seated in a chair. The program ran for 8 1-hour weekly sessions via Zoom. Control n=19 Wait list			
Ehde 2015[13] RCT N=163 Conducted in USA	Telephone-delivered self-management programme n= 75 8 weekly 45-60 min telephone sessions. Cognitive behavioural and positive psychology strategies to help self-manage pain, depression and fatigue in daily lives. At final session a comprehensive self-management plan was created integrating preferred skills and goals for use post-treatment. Control n=88 8 weekly 45-60 min telephone sessions. Telephone education programme covering topics such as fatigue, pain and nutrition.	Multiple sclerosis Pain type: chronic Age: mean 51.0-53.0 years across the two groups Type of MS: Majority had relapsing-remitting MS (>50% in both groups) EDSS: majority (>60% in both groups) had EDSS score 4.5-6.0	Pain interference (BPI) Pain intensity (NRS) Physical HRQoL (SF-8) Mental HRQoL (SF-8)	
Gromisch 2020[14] RCT N= 20 Conducted in USA	CBT plus standard care n=10 Twelve sessions, including seven 60-minute, outpatient, individual sessions and five 30-minute individual telephone sessions	Multiple sclerosis Pain type: neuropathic pain, pain related to muscle	Pain severity To minimize type I errors due to multiple comparisons, a Pain Severity Composite	

Study	Intervention and comparison	Population	Relevant outcomes	Comments
	delivered by clinical health psychologists. Components of CBT treatment included 1) identification of idiosyncratic beliefs about pain and pain treatment, 2) instruction in cognitive (eg, distraction) and behavioural (eg, activity pacing) skills, and 3) consolidation of cognitive and behavioural skills through activities such as role-playing MS-related education plus standard care n=10 Twelve sessions, including seven 60-minute, outpatient, individual sessions and five 30-minute individual telephone sessions delivered by clinical health psychologists. Topics for the 12 sessions include information on MS aetiology, diagnosis and prognosis, pain in MS, medications for symptom management, disease-modifying medications, alternative therapies, rehabilitation, exercise, lifestyle issues, alcohol use and smoking, preventive health, adapting the home and assistive devices, and caregiver support.	spasms and neuralgias were part of the inclusion criteria Mean age (SD): 52.6 (10.95) Type of MS (n): 14 relapsing remitting MS, 4 progressive relapsing, 2 primary progressive MS EDSS not reported	Score was created using the NRS, the WHYMPI Pain Severity subscale, and the McGill Evaluative subscale, Pain interference WHYMPI - interference subscale Beck Depression Inventory	
Grubic Kezele 2020[15] Grubic Kezele 2019[16] RCT	Upper limb and breathing exercises n=10 Two sessions per week (60 min per session) under physiotherapist	Multiple sclerosis Pain type: not reported	Barthel index (0-100) Visual Analogue Scale (VAS 0-5) for pain	Small feasibility study

Study	Intervention and comparison	Population	Relevant outcomes	Comments
N=19 Conducted in Croatia	supervision in addition to independent home exercise three days a week (at least 20 min per session) for 4 weeks. Exercises performed sitting in chair. Range of motions, resistance level and exercise speed was individualised to each person. 30-60 second pause after each exercise. Began with 15 min warm-up of breathing and active mobility of upper limbs. Breathing aimed to strengthen abdominal muscles, diaphragm and intercostal muscles. Exercises included range movement, coordination and strengthening with minimal resistance. Control n=9 No exercise. Required to visit centre two times weekly (up to 60 min) where they could socialise and have contact with the investigators. Any existing exercise unchanged.	Overall mean age not reported but inclusion criteria was adults 18-70 years Exercise group Mean age (SD): 53.9 (10.7) years MS type: relapsing-remitting 4, primary progressive 2, secondary progressive 4 Median EDSS (IQR), 6.5 (1.0-8.0) Control group: Mean age (SD), 53.9 (10.7) years MS type: relapsing-remitting 6, Primary progressive 0, secondary progressive 3 Median EDSS (IQR), 7.0 (1.0-7.5)		
Hasanpour-Dehkordi 2016[17, 18] ENREF 18 RCT N=60 randomised across 3 groups Conducted in Iran	Yoga n=30 Three sessions weekly for 12 weeks. Hatha yoga classes 60-70 min in duration. Included postures, breathing techniques and meditation. Postures started with stretching techniques followed by, standing, supine and prone-lying and sitting procedures. Each pose	Multiple sclerosis Mean Age (SD): 31.9 (NR) Pain type, MS type and EDSS scores: not reported	SF-36 Quality of Life Questionnaire	

Study	Intervention and comparison	Population	Relevant outcomes	Comments
	held for 10-30 seconds with rest periods in between of 30 seconds to 1 min. Each session ended with 10 min deep relaxation. Practice at home advised and given a booklet explaining the poses. Aerobic exercise n=30 Three sessions weekly for 12 weeks. Each session lasted 40 min, with 5-10 min warm-up, 25-30 min exercise (walking) and 5 min cooling down. Exercise aimed to reach 60% of heart rate reserve. After 6 sessions duration of exercise increased to 30-35 min at a heart rate of 70% heart rate reserve. Control n=30 Educational support with no exercise protocol. Asked to continue medications and usual lifestyle.			
Hughes 2009[19] RCT N= 71 Conducted in Northern Ireland	Precision reflexology n=35 Reflexology consisting of a sequence of pressure massage which allowed stimulation of all of the key reflex points on the feet associated with organs throughout the body. Sham reflexology n=36 a standardised foot massage using the same predefined sequence in	Multiple sclerosis Pain type: musculoskeletal (low back pain, legs, feet, shoulders, hips arms, eyes) Precision reflexology Mean age (SD) 50 (11.1) MS type: benign 0, relapsing-	Pain VAS (0-10) MSIS-29 Beck Depression Inventory	Included in the previous guideline Results presented as Medians and IQR and could not be meta-analysed in Review Manager software

Study	Intervention and comparison	Population	Relevant outcomes	Comments
	order to provide a sham treatment. Using less pressure and avoiding common areas of pain associated with MS.	remitting 16, primary-progressive 4, secondary progressive 6, not known 9 Sham reflexology Mean age (SD) 53 (11.0) MS type: benign 1; relapsing-remitting 12; primary-progressive 4; secondary progressive 6; not known 9. EDSS: not reported		
Jensen 2009[20] Quasi-RCT N=22 Conducted in USA	Self-hypnosis training n=15 Hypnosis sessions led by a physician including suggestions of analgesia and comfort as well as self-administered hypnosis sessions at home using audio recordings. Progressive muscle relaxation n=7 Ten sessions involving progressive tightening and relaxing of different muscle groups with ongoing suggestions that this would be associated with an increased sense of relaxation and comfort.	Multiple sclerosis Pain type: only reports that participants had chronic Mean age 51.7 #9range 27-75 years) EDSS not reported	Pain intensity (NRS) Pain interference (modified BDI score)	
Jensen 2018[21] RCT N=35 Randomised across 3 groups Conducted in USA	Self-hypnosis + neurofeedback n=12 Six sessions (over 3 weeks) of theta-enhancing neurofeedback training (individually provided in person in the clinic),	Multiple sclerosis Pain type: not reported Mean age (SD) 57.53 (10.63)	Average pain intensity (NRS 0-10) Pain interference (BPI) Pain catastrophising	

Study	Intervention and comparison	Population	Relevant outcomes	Comments
	followed by single face-to-face hypnosis session and then 4 sessions of neurofeedback just before 4 audiotaped additional self-hypnosis training. Self-hypnosis + mindfulness meditation n=12 Six sessions (over 3 weeks) of mindfulness training, followed by single face-to-face hypnosis session just before and then 4 sessions of mindfulness just before 4 audiotaped additional self-hypnosis training. Hypnosis alone (control) n=11 Three weeks waiting period followed by a single face-to-face hypnosis session and then 4 audiotaped additional self-hypnosis training.	Type of MS (n): 17 relapsing remitting, secondary progressive 6, primary progressive 3, progressive relapsing 0, uncertain 6	(PCS) Pain acceptance (CPAQ) Sleep disturbance	
Masoudi 2013[22] RCT N=70 Conducted in Iran	Progressive Muscle Relaxation Technique (PMRT) n=35 An educational package was initially implemented. This included explaining the different muscles and muscle groups involved in the techniques, participants implementing the techniques in the presence of a researcher and predicting what participants might feel physically and mentally after implementation. Patients were then instructed to practice the techniques at home,	Multiple sclerosis Age Of those aged 20-30 years, 20 in the control group and 18 in the experimental group Of those aged 31-40 years: 15 in the control group and 17 in the experimental MS type, pain type and	VAS (0-10) for pain	Included in previous guideline

Study	Intervention and comparison	Population	Relevant outcomes	Comments
	once every day over a 3-month period with the help of an instructional CD. The exercises involved tensing and relaxing different muscle groups, breathing deeply and effectively at the same time. Control n=35 Participants were introduced to a relaxation technique in a single session.	EDSS scores not reported		
Mori 2010[23] RCT N=19 Conducted in Italy	Anodal tDCS, A constant current of 2mA current was applied for 20 minutes once a day for 5 consecutive days n=10 Sham tDCS n=9 Electrodes placed in the same positions as for anodal tDCS but the stimulator was turned off after 30 seconds of stimulation.	Multiple sclerosis N=19 Pain type: neuropathic pain Mean age 44.8 (27.5) years; 11 females/8 males. Mean 42.8 years (5 females, 5 males) in active treatment group and 46.3 years (6 females, 3 males) in sham group.	Pain VAS (0-100) Anxiety VAS (0-100) Short Form McGill Questionnaire, MSQOL Beck Depression Inventory	Included in previous guideline Authors report results graphically in forest plots and diagrams. No data could be extracted.
Nazari 2015[25] RCT N=75 randomised across 3 groups Conducted in Iran	Relaxation n=25 Twice weekly sessions for 4 weeks (40 min per session). Performed in bright, silent, warm room. Combination of Jacobson and Benson methods for those receiving relaxation. Reflexology n=25	Multiple sclerosis Age: mean 34.0 years for all three groups Pain type and MS type: not reported	Pain Numerical Rating Scale (NRS)	

Study	Intervention and comparison	Population	Relevant outcomes	Comments
	For those that had reflexology, general reflex therapy was performed by massaging all plantar reflexology points followed by special reflex therapy. Major reflex points in feet under pressure using thumb and index finger. Ended with massage of solar plexus. Control n=25 Routine treatment and care recommended by attending physician.	EDSS: score between 0.0 and 5.5 was an inclusion criterion.		
Negahban 2013[27] RCT N=48 randomised across the 4 groups Conducted in Iran	Exercise alone n=12 Combined set of strength, stretch, endurance and balance training exercises Massage alone n=12 Three 30 min supervised intervention sessions per week for 5 weeks Swedish massage by trained massage therapist. Massage + exercise n=12 Three 30 min supervised intervention sessions per week for 5 weeks. Passive massage for 15 min and encouraged to perform active exercises of those included in the exercise therapy group. Time split between the two so that it did not exceed 30 min. Control n=12	Multiple sclerosis Pain type: not reported Mean age (SD) across the groups: 36.6 (7.45) EDSS mean (SD): 3.7 (1.3) MS type: relapsing-remitting MS or secondary progressive MS was an inclusion criterion. Proportion with each not reported.	VAS (0-10) for pain Multiple Sclerosis Quality of Life-54 (MSQOL-54) –	

Study	Intervention and comparison	Population	Relevant outcomes	Comments
	Continue standard medical care and asked to avoid participation in any new exercise programme or change usual activities for 5 weeks			
Palm 2016[31] Cross over RCT N=16 Conducted in France	Transcranial random noise stimulation (tRNS) n=8 Sham tRNS n=8	Multiple sclerosis Pain type: neuropathic pain 16 randomised (number in each group was not reported) Age: mean age 47.4 years, age range 38-64 years	Pain VAS (0-100) BPI HADS	Wash out period was 3 weeks
Pilutti 2014[33] RCT N=82 Conducted in the USA	Behavioural intervention designed to increase physical activities n=41 Internet-based intervention which included several components, namely a dedicated study website with information about becoming more physically active based on principles of social cognitive theory (SCT), self-monitoring and goalsetting using a pedometer and activity logs, and one-on one web-based video coaching sessions. Control n= 41 No intervention	Multiple sclerosis Pain type: not reported Mean age (SD): Intervention 48.4 (9.1), Control 49.5 (9.2) MS type: Intervention group: relapsing remitting 31, secondary progressive 8, primary progressive 2 Control group: relapsing remitting 34, secondary progressive 2,	MSIS29 HADS Short-form McGill Pain Questionnaire (SF-MPQ) The Pittsburgh Sleep Quality Index (PSQI)	

Study	Intervention and comparison	Population	Relevant outcomes	Comments
		primary progressive 5 EDSS: not reported		
Warke 2006[34] RCT N=90 Conducted in Northern Ireland	Low frequency TENS n=30 4 Hz, 200µs 45 minutes twice a day and at any time when a painful episode occurred for 6 weeks High frequency TENS n=30 110 Hz, 200µs 45 minutes twice a day and at any time when a painful episode occurred for 6 weeks Placebo TENS n=30 45 minutes twice a day and at any time when a painful episode occurred for 6 weeks	Multiple sclerosis Pain type: low back pain Age range 37 to 71 years. MS type: not reported EDSS: not reported	VAS (0-10) McGill Pain Questionnaire Barthel Index MSQOL Leeds Multiple Sclerosis Quality of Life	Extension of Warke 2004 which was included in the previous guideline Authors present results graphically and in narrative and have therefore been summarised narratively in this review
Young 2019[36] N= 81 randomised across 3 groups Conducted in USA	Movement to music (M2M) n=27 Three 60-minute exercise sessions per week for 12 weeks. Adapted Yoga n=26 Three 60-minute exercise sessions per week for 12 weeks. Waitlist control n=28 Waitlist controls received biweekly newsletters via mail that contained educational information on living with MS.	Multiple sclerosis Age range: 18-65 years Mean age (SD): 48.38 (9.82) Pain type, MS type and EDSS scores: not reported	Pain interference (SF-8)	
Young 2020[37] RCT	Anodal tDCS n=30	Multiple sclerosis	Pain VAS (0-10) DASS	

Study	Intervention and comparison	Population	Relevant outcomes	Comments
N=30 Conducted in Australia	A constant current of 2mA was applied for 10 minutes stimulation, 25 minutes of non-stimulation and then another 10 minutes of stimulation at approximately the same time for 5 consecutive days Sham n=30 Same set up as intervention group but stimulation was turned on for 30 seconds then ramped down to no stimulation.	Pain type: most commonly reported site of pain was unilateral or bilateral lower limb pain tDCS Mean age (SD) 51.2 (9.3) MS type: relapsing remitting 9, secondary progressive 3, primary progressive 1 Sham Mean age (SD) 48.87 (12.9) MS type: relapsing remitting 7, secondary progressive 6, primary progressive 2 EDSS not reported	MSQOL54-mental MSQOL54-physical	

1 See Appendix D for full evidence tables.

2

1.1.6 Summary of the effectiveness evidence

See Appendix F for full GRADE tables

Yoga vs control or waitlist

Table 3: Clinical evidence summary: Yoga vs control or waitlist

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control or waitlist	Risk difference with Yoga
SF-36 Quality of life (0-100 for each domain; higher is better outcome) - SF-36 Body Pain follow-up: 12 weeks	40 (1 RCT)	⊕◯◯◯ Very low [a,b,c]	-	The mean SF-36 Quality of life (0-100 for each domain; higher is better outcome) - SF-36 Body Pain was 55.71	MD 17.17 lower (22.97 lower to 11.37 lower)
SF-36 Quality of life (0-100 for each domain; higher is better outcome) - SF-36 Mental Health follow-up: 12 weeks	40 (1 RCT)	⊕◯◯◯ Very low [a,b,d]	-	The mean SF-36 Quality of life (0-100 for each domain; higher is better outcome) - SF-36 Mental Health was 50.44	MD 10.1 higher (1.15 higher to 19.05 higher)
SF-36 Quality of life (0-100 for each domain; higher is better outcome) - SF-36 Limited Activity following physical problems follow-up: 12 weeks	40 (1 RCT)	⊕◯◯◯ Very low [a,b,e]	-	The mean SF-36 Quality of life (0-100 for each domain; higher is better outcome) - SF-36 Limited Activity following physical problems was 52.14	MD 6.69 lower (14.08 lower to 0.7 higher)
SF-36 Quality of life (0-100 for each domain; higher is better outcome) - SF-36 General Health follow-up: 12 weeks	40 (1 RCT)	⊕◯◯◯ Very low [a,b,f]	-	The mean SF-36 Quality of life (0-100 for each domain; higher is better outcome) - SF-36 General Health was 42.65	MD 8.57 higher (3.02 higher to 14.12 higher)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control or waitlist	Risk difference with Yoga
Pain (MSQoL-54, 0-10 scale, higher is better outcome) follow-up: 4 weeks	60 (1 RCT)	⊕◯◯◯ Very low[a,b,g]	-	The mean pain (MSQoL-54, 0-10 scale, higher is better outcome) was 3.3	MD 0.5 higher (1.62 lower to 2.62 higher)
Quality of Life at 1 month (MSQoL-54, 0-10 scale, higher is better outcome) follow-up: 4 weeks	60 (1 RCT)	⊕◯◯◯ Very low [a,b,h]	-	The mean quality of Life at 1 month (MSQoL-54, 0-10 scale, higher is better outcome) was 6.8	MD 0.6 higher (0.43 lower to 1.63 higher)
Pain interference (PROMIS Interference short form 8a) follow-up: 12 weeks	54 (1 RCT)	⊕◯◯◯ Very low [a,b,i]	-	The mean pain interference (PROMIS Interference short form 8a) was 51.7	MD 1.6 higher (2.96 lower to 6.16 higher)
Additional study – that could not be analysed in Review Manager or GRADE:					
An additional (Dunne 2021), which was a small (N=53) mixed methods study comparing Chair Yoga to Mindfulness for MS program (M4M) or to control did not find any statically significant differences in any of the MSQoL-54 or BPI scales. It only reported medians and IQR and therefore could not be analysed in Review Manager or GRADE [High risk of bias for methodological quality]					

a. 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

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

c. MIDs used to assess imprecision were ±4.38

d. MIDs used to assess imprecision were ±7.56

e. MIDs used to assess imprecision were ±6.32

f. MIDs used to assess imprecision were ±4.75

g. MIDs used to assess imprecision were ±2.3

h. MIDs used to assess imprecision were ±0.85

i. MIDs used to assess imprecision were ±4.7

Yoga compared to Movement to Music (M2M) Exercise for pain in MS

Table 4: Clinical evidence summary: Yoga compared to Movement to Music (M2M) Exercise for pain in MS

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with M2M Exercise	Risk difference with Yoga
Pain interference (PROMIS Interference short form 8a) follow-up: 12 weeks	53 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	-	The mean pain interference (PROMIS Interference short form 8a) was 53.1	MD 0.2 higher (4.81 lower to 5.21 higher)

a. 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

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

c. MIDs used to assess imprecision were ±4.7

M2M exercise vs control

Table 5: Clinical evidence summary: Movement to Music (M2M) vs control

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Movement to Music (M2M)
Pain interference (PROMIS Interference short form 8a)	55 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	-	The mean pain interference (PROMIS Interference short form 8a) was 52.6	MD 1.4 higher (3.75 lower to 6.55 higher)

a. 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

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

c. MIDs used to assess imprecision were ±4.9

Exercise (strength, stretch, endurance and balance) compared to control

Table 6: Clinical evidence summary: Exercise (strength, stretch, endurance and balance) compared to control

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with Exercise (strength, stretch, endurance and balance)
Pain (VAS 0-10, Lower is better outcome) follow-up: 5 weeks	24 (1 RCT)	⊕⊕◯◯ Low[a,b,c]	-	The mean pain (VAS 0-10, Lower is better outcome) was 4.83	MD 3.42 lower (5.1 lower to 1.74 lower)

a. 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

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

c. MIDs used to assess imprecision were ±2.02

Aerobic exercise vs control

Table 7: Clinical evidence summary: Aerobic exercise vs control

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with Aerobic exercise
SF-36 Quality of life (0-100 for each domain; higher is better outcome) - SF-36 Body Pain follow-up: 12 weeks	41 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	-	The mean SF-36 Quality of life (0-100 for each domain; higher is better outcome) - SF-36 Body Pain was 0	MD 16.06 lower (22.42 lower to 9.7 lower)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with Aerobic exercise
SF-36 Quality of life (0-100 for each domain; higher is better outcome) - SF-36 Mental Health follow-up: 12 weeks	41 (1 RCT)	⊕◯◯◯ Very low[a,b,d]	-	The mean SF-36 Quality of life (0-100 for each domain; higher is better outcome) - SF-36 Mental Health was 0	MD 11.34 higher (3.54 higher to 19.14 higher)
SF-36 Quality of life (0-100 for each domain; higher is better outcome) - SF-36 Limited Activity following physical problems follow-up: 12 weeks	41 (1 RCT)	⊕◯◯◯ Very low[a,b,e]	-	The mean SF-36 Quality of life (0-100 for each domain; higher is better outcome) - SF-36 Limited Activity following physical problems was 0	MD 6 lower (13.93 lower to 1.93 higher)
SF-36 Quality of life (0-100 for each domain; higher is better outcome) - SF-36 General Health follow-up: 12 weeks	41 (1 RCT)	⊕⊕◯◯ Low[a,f]	-	The mean SF-36 Quality of life (0-100 for each domain; higher is better outcome) - SF-36 General Health was 0	MD 12.58 higher (6.36 higher to 18.8 higher)

a. 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

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

c. MIDs used to assess imprecision were ±4.73

d. MIDs used to assess imprecision were ±3.77

e. MIDs used to assess imprecision were ±7.07

f. MIDs used to assess imprecision were ±4.24

Aerobic exercise vs yoga

Table 8: Clinical evidence summary: Aerobic exercise vs yoga

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with yoga	Risk difference with Aerobic exercise
SF-36 Quality of life (0-100 for each domain; higher is better outcome) - SF-36 Body Pain follow-up: 12 weeks	41 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	-	The mean SF-36 Quality of life (0-100 for each domain; higher is better outcome) - SF-36 Body Pain was 0	MD 1.11 higher (5.19 lower to 7.41 higher)
SF-36 Quality of life (0-100 for each domain; higher is better outcome) - SF-36 Mental Health follow-up: 12 weeks	41 (1 RCT)	⊕◯◯◯ Very low[a,b,d]	-	The mean SF-36 Quality of life (0-100 for each domain; higher is better outcome) - SF-36 Mental Health was 0	MD 1.24 higher (6.56 lower to 9.04 higher)
SF-36 Quality of life (0-100 for each domain; higher is better outcome) - SF-36 Limited Activity following physical problems follow-up: 12 weeks	41 (1 RCT)	⊕◯◯◯ Very low[a,b,e]	-	The mean SF-36 Quality of life (0-100 for each domain; higher is better outcome) - SF-36 Limited Activity following physical problems was 0	MD 0.69 higher (6.67 lower to 8.05 higher)
SF-36 Quality of life (0-100 for each domain; higher is better outcome) - SF-36 General Health follow-up: 12 weeks	41 (1 RCT)	⊕◯◯◯ Very low[a,b,f]	-	The mean SF-36 Quality of life (0-100 for each domain; higher is better outcome) - SF-36 General Health was 0	MD 4.01 higher (2.05 lower to 10.07 higher)

a. 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

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

c. MIDs used to assess imprecision were ±3.84

d. MIDs used to assess imprecision were ±5.55

e. MIDs used to assess imprecision were ±3.21

f. MIDs used to assess imprecision were ±5.3

Behavioural intervention to increase lifestyle activity vs control

Table 9: Clinical evidence summary: Behavioural intervention to increase lifestyle activity vs control

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with Behavioural intervention to increase lifestyle activity
Pain (SF-MPQ 0-45, lower is better outcome) follow-up: 6 months[i]	76 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	-	The mean pain (SF-MPQ 0-45, lower is better outcome) was 9.8	MD 1.7 lower (3.51 lower to 0.11 higher)
HADS anxiety follow-up: 6 months	76 (1 RCT)	⨁◯◯◯ Very low[a,b,d]	-	The mean HADS anxiety was 5.6	MD 1.5 lower (2.61 lower to 0.39 lower)
HADS depression follow-up: 6 months	76 (1 RCT)	⨁⨁◯◯ Very low[a,b,e]	-	The mean HADS depression was 6.6	MD 1.6 lower (2.71 lower to 0.49 lower)
PSQI Global Sleep Disturbance follow-up: 6 months[i]	76 (1 RCT)	⨁◯◯◯ Very low[a,b,f]	-	The mean PSQI Global Sleep Disturbance was 7.4	MD 1 lower (2.1 lower to 0.1 higher)
MSIS-29 Physical follow-up: 6 months[i]	76 (1 RCT)	⨁⨁◯◯ Low[a, g]	-	The mean MSIS-29 Physical was 33.2	MD 4.1 lower (8.26 lower to 0.06 higher)
MSIS 29 psychological follow-up: 6 months[i]	76 (1 RCT)	⨁◯◯◯ Very low[a,b,h]	-	The mean MSIS 29 psychological was 33.1	MD 5.5 lower (12.02 lower to 1.02 higher)

a. 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

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

c. MIDs used to assess imprecision were ±3.68

d. MIDs used to assess imprecision were ±1.87

e. MIDs used to assess imprecision were ±2.02

f. MIDs used to assess imprecision were ±2.1

g. MIDs used to assess imprecision were ±12.4

h. MIDs used to assess imprecision were ±11.22

i. Baseline differences observed: Pain: Intervention 8.3 (7) and control 10.6 (7.7); PSQI global sleep disturbance: Intervention 6.9 (4.1) and control 8.4 (4.3); MSIS-29 physical: intervention 28.6 (25.1) and control 34.5 (24.5); MSIS 29 psychological: intervention 27.2 (21.4) and control 33.7 (23.4)

Upper limb and breathing exercise vs control

Table 10: Clinical evidence summary: Upper limb and breathing exercise vs control

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with Upper limb and breathing exercise
Pain (VAS 0-5, lower is better outcome) follow-up: 4 weeks	19 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	-	The mean pain (VAS 0-5, lower is better outcome) was 3.4	MD 2 lower (4.04 lower to 0.04 higher)
Barthel Index (0-100, higher is better outcome) follow-up: 4 weeks	19 (1 RCT)	⊕◯◯◯ Very low[a,b,d]	-	The mean barthel Index (0-100, higher is better outcome) was 75.91	MD 1.99 higher (14.52 lower to 18.50 higher)
SF-36 Quality of life (0-100 for each domain; higher is better outcome) - General Health domain follow-up: 4 weeks	19 (1 RCT)	⊕◯◯◯ Very low[a,b,e]	-	The mean SF-36 Quality of life (0-100 for each domain; higher is better outcome) - General Health domain was 41.1	MD 8.4 higher (8.96 lower to 25.76 higher)
SF-36 Quality of life (0-100 for each domain; higher is better outcome) - Pain domain follow-up: 4 weeks	19 (1 RCT)	⊕◯◯◯ Very low[a,b,f]	-	The mean SF-36 Quality of life (0-100 for each domain; higher is better outcome) - Pain domain was 64.2	MD 12.1 higher (17.41 lower to 41.61 higher)
SF-36 Quality of life (0-100 for each domain; higher is better outcome) - Physical Functioning domain follow-up: 4 weeks	19 (1 RCT)	⊕◯◯◯ Very low[a,b,g]	-	The mean SF-36 Quality of life (0-100 for each domain; higher is better outcome) - Physical Functioning domain was 43.9	MD 5.4 lower (41.29 lower to 30.49 higher)
SF-36 Quality of life (0-100 for each domain; higher is better outcome) - Physical Limitations domain follow-up: 4 weeks	19 (1 RCT)	⊕◯◯◯ Very low[a,b,h]	-	The mean SF-36 Quality of life (0-100 for each domain; higher is better outcome) - Physical Limitations domain was 44.4	MD 5.6 higher (28.3 lower to 39.5 higher)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with Upper limb and breathing exercise
SF-36 Quality of life (0-100 for each domain; higher is better outcome) - Emotional Wellbeing domain follow-up: 4 weeks	19 (1 RCT)	⨁◯◯◯ Very low[a,b,i]	-	The mean SF-36 Quality of life (0-100 for each domain; higher is better outcome) - Emotional Wellbeing domain was 64	MD 11.6 higher (4.01 lower to 27.21 higher)
SF-36 Quality of life (0-100 for each domain; higher is better outcome) - Emotional Limitations domain follow-up: 4 weeks	19 (1 RCT)	⨁◯◯◯ Very low[a,b,j]	-	The mean SF-36 Quality of life (0-100 for each domain; higher is better outcome) - Emotional Limitations domain was 59.1	MD 27.6 higher (7.32 lower to 62.52 higher)

a. 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

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

c. MIDs used to assess imprecision were ±1.2

d. MIDs used to assess imprecision were ±3.47

e. MIDs used to assess imprecision were ±9.62

f. MIDs used to assess imprecision were ±18

g. MIDs used to assess imprecision were ±18.82

h. MIDs used to assess imprecision were ±17.52

i. MIDs used to assess imprecision were ±10.42

j. MIDs used to assess imprecision were ±20.47

Progressive muscle relaxation technique vs control

Table 11: Clinical evidence summary: Progressive muscle relaxation technique vs control

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with Progressive muscle relaxation technique
Pain at 3 months (VAS 0-10; lower indicates better outcome) follow-up: 3 months	70 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	-	The mean pain at 3 months (VAS 0-10; lower indicates better outcome) was 8.14	MD 4.17 lower (4.82 lower to 3.52 lower)

a. 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

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

c. MIDs used to assess imprecision were ±0.74

Relaxation compared to control

Table 12: Clinical evidence summary: Relaxation compared to control

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with Relaxation
Pain (NRS, lower indicates better outcomes) follow-up: 2 months	50 (1 RCT)	⊕⊕◯◯ Low[a,b,c]	-	The mean pain (NRS, lower indicates better outcomes) was 5.32	MD 0.16 lower (1.1 lower to 0.78 higher)

a. 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

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

c. MIDs used to assess imprecision were ±0.86

Reflexology compared to control

Table 13: Clinical evidence summary: Reflexology compared to control

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with Reflexology
Pain (NRS, lower indicates better outcomes) follow-up: 2 months	50 (1 RCT)	⊕⊕◯◯ Low[a,b,c]	-	The mean pain (NRS, lower indicates better outcomes) was 5.32	MD 0.68 lower (1.75 lower to 0.39 higher)

a. 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

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

c. MIDs used to assess imprecision were ±0.95

A study by Hughes 2009[19] compared precision reflexology with sham reflexology (standardised foot massage avoiding points representative of common areas of pain associated with MS). Outcomes were presented as median (IQR) rather than means and standard deviations making the data unsuitable for RevMan analysis. The authors reported that a significant and clinically important decrease in pain intensity was observed in both groups compared with baseline; median VAS Pain scores were reduced by 50% following treatment and were maintained for up to 12 weeks. However, there was no significant difference between the groups for this outcome. Significant decreases were also observed for, depression and quality of life. Precision reflexology was not superior to sham, but the authors suggest that the improvement in symptoms might be due to a placebo effect or stimulation of reflex points in the feet using the non-specific massage. [High risk of bias for methodological quality]

Massage compared to control for pain in MS

Table 14: Clinical evidence summary: Massage compared to control for pain in MS

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with Massage
Pain at 5 weeks (VAS 0-10; lower is better outcome) follow-up: 5 weeks	24 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	-	The mean pain at 5 weeks (VAS 0-10; lower is better outcome) was 4.83	MD 3.08 lower (4.96 lower to 1.2 lower)

a. 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

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

c. MIDs used to assess imprecision were ±1.14

Relaxation compared to reflexology for pain in MS

Table 15: Clinical evidence summary: Relaxation compared to reflexology

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with reflexology	Risk difference with Relaxation
Pain (NRS, lower indicates better outcomes) follow-up: 2 months	50 (1 RCT)	⊕⊕◯◯ Low[a,b,c]	-	The mean pain (NRS, lower indicates better outcomes) was 4.64	MD 0.52 higher (0.54 lower to 1.58 higher)

a. 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

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

c. MIDs used to assess imprecision were ±0.9

Exercise compared to Massage

Table 16: Clinical evidence summary: Exercise compared to Massage

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Massage	Risk difference with Exercise
Pain (VAS 0-10; lower is better outcome) follow-up: 5 weeks	24 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	-	The mean pain (VAS 0-10; lower is better outcome) was 1.75	MD 0.34 lower (1.65 lower to 0.97 higher)

a. 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

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

c. MIDs used to assess imprecision were ±0.97

Massage + exercise compared to control

Table 17: Clinical evidence summary: Massage + exercise compared to control

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with Massage + exercise
Pain (VAS 0-10; lower is better outcome) follow-up: 5 weeks	24 (1 RCT)	⊕⊕◯◯ Low[a,b,c]	-	The mean pain (VAS 0-10; lower is better outcome) was 4.83	MD 2.17 lower (3.94 lower to 0.4 lower)

a 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

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

c. MIDs used to assess imprecision were ±1.02

Massage + exercise compared to massage alone for pain in MS

Table 18: Massage + exercise compared to massage alone for pain in MS

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with massage alone	Risk difference with Massage + exercise
Pain (VAS 0-10; lower is better outcome) follow-up: 5 weeks	24 (1 RCT)	⊕⊕◯◯ Low[a,b,c]	-	The mean pain (VAS 0-10; lower is better outcome) was 1.75	MD 0.91 higher (0.52 lower to 2.34 higher)

a. 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

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

c. MIDs used to assess imprecision were ±0.89

MS Education program (ENGAGE) vs Usual care

Table 19: Clinical evidence summary: MS Education program (ENGAGE) vs Usual care

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with MS Education program (ENGAGE)
Pain Catastrophising (PCS) follow-up: 3 months	27 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	-	The mean pain Catastrophising (PCS) was 14.42	MD 4.14 higher (3.74 lower to 12.02 higher)
Pain intensity (NRS) follow-up: 3 months	27 (1 RCT)	⊕◯◯◯ Very low[a,b,d]	-	The mean pain intensity (NRS) was 3.58	MD 0.08 lower (1.43 lower to 1.27 higher)
Pain interference (PROMIS) follow-up: 3 months	27 (1 RCT)	⊕◯◯◯ Very low[a,b,e]	-	The mean pain interference (PROMIS) was 55.23	MD 0.15 higher (5.91 lower to 6.21 higher)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with MS Education program (ENGAGE)
Depression (PHQ-8) follow-up: 3 months	27 (1 RCT)	⨁◯◯◯ Very low[a,b,f]	-	The mean depression (PHQ-8) was 6.41	MD 2.03 higher (0.61 lower to 4.67 higher)

a. 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

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

c. MIDs used to assess imprecision were ±4.5

d. MIDs used to assess imprecision were ±0.79

e. MIDs used to assess imprecision were ±3.11

f. MIDs used to assess imprecision were ±1.51

Self-management Programme vs control

Table 20: Clinical evidence summary: Self-management Programme vs control

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with Self-Management Programme
Pain intensity (NRS 0-10, lower is better outcome) follow-up: 6 months	163 (1 RCT)	⨁⨁⨁◯ Moderate[a,b]	-	The mean pain intensity (NRS 0-10, lower is better outcome) was 3.1	MD 0.2 higher (0.48 lower to 0.88 higher)
Pain Interference (BPI 0-10, lower is better outcome) follow-up: 6 months	163 (1 RCT)	⨁⨁⨁◯ Moderate[a,c]	-	The mean pain Interference (BPI 0-10, lower is better outcome) was 3	MD 0.2 lower (0.95 lower to 0.55 higher)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with Self-Management Programme
Depression (PHQ-9 0-27, lower is better outcome) follow-up: 6 months	163 (1 RCT)	⊕⊕◯◯ Low[a,d,e]	-	The mean depression (PHQ-9 0-27, lower is better outcome) was 6.7	MD 1 lower (2.38 lower to 0.38 higher)
HRQoL Physical (SF-8) follow-up: 6 months	163 (1 RCT)	⊕⊕⊕◯ Moderate[a,f]	-	The mean hRQoL Physical (SF-8) was 40.4	MD 0.1 lower (2.98 lower to 2.78 higher)
HRQoL Mental (SF-8) follow-up: 6 months	163 (1 RCT)	⊕⊕⊕◯ Moderate[a,d,g]	-	The mean hRQoL Mental (SF-8) was 47	MD 1.2 higher (1.78 lower to 4.18 higher)

a. 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

b. MIDs used to assess imprecision were ±1

c. MIDs used to assess imprecision were ±102

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

e. MIDs used to assess imprecision were ±2.07

f. MIDs used to assess imprecision were ±4.02

g. MIDs used to assess imprecision were ±4.62

Hypnosis + neurofeedback vs hypnosis alone

Table 21: Clinical evidence summary: Hypnosis + neurofeedback vs hypnosis alone

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Hyp alone	Risk difference with Hyp + neurofeedback
Average Pain Intensity (NRS 0-10, lower is better outcome) follow-up: 1 months	11 (1 RCT)	⊕⊕◯◯ Low[a,b,c]	-	The mean average Pain Intensity (NRS 0-10, lower is better outcome) was 4.48	MD 2.06 lower (4.2 lower to 0.08 higher)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Hyp alone	Risk difference with Hyp + neurofeedback
Pain interference (BPI, lower is better) follow-up: 1 months	11 (1 RCT)	⊕⊕◯◯ Low[a,d]	-	The mean pain interference (BPI, lower is better) was 4.69	MD 2.67 lower (5.56 lower to 0.22 higher)
Pain catastrophising (PCS) follow-up: 1 months	11 (1 RCT)	⊕◯◯◯ Very low[a,b,e]	-	The mean pain catastrophising (PCS) was 14.8	MD 5.63 lower (18.81 lower to 7.55 higher)
Pain acceptance (CPAQ) follow-up: 1 months	11 (1 RCT)	⊕⊕◯◯ Low[a,b,f]	-	The mean pain acceptance (CPAQ) was 72.4	MD 10.27 higher (2.52 lower to 23.06 higher)
Depression follow-up: 1 months	22 (1 RCT)	⊕◯◯◯ Very low[a,b,g]	-	The mean depression was 0	MD 1.37 lower (5.48 lower to 2.74 higher)
Sleep disturbance follow-up: 1 months	22 (1 RCT)	⊕◯◯◯ Very low[a,b,h]	-	The mean sleep disturbance was 52.84	MD 2.61 lower (10.01 lower to 4.79 higher)

a. 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

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

c. MIDs used to assess imprecision were ±0.68

d. MIDs used to assess imprecision were ±0.69

e. MIDs used to assess imprecision were ±4.47

f. MIDs used to assess imprecision were ±9.42

g. MIDs used to assess imprecision were ±2.11

h. MIDs used to assess imprecision were ±4.21

Hypnosis + neurofeedback vs hypnosis +Mindfulness (at 1 month)

Table 22 Clinical evidence summary: Hypnosis + neurofeedback vs hypnosis +Mindfulness (at 1 month)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Hyp +Mindfulness (at 1 month)	Risk difference with Hyp + neurofeedback
Average Pain Intensity (NRS 0-10, lower is better outcome) follow-up: 1 months	10 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	-	The mean average Pain Intensity (NRS 0-10, lower is better outcome) was 3.31	MD 0.89 lower (2.48 lower to 0.7 higher)
Pain interference (BPI, lower is better) follow-up: 1 months	10 (1 RCT)	⊕⊕◯◯ Low[a,b,d]	-	The mean pain interference (BPI, lower is better) was 3.43	MD 1.41 lower (3.03 lower to 0.21 higher)
Pain catastrophising (PCS) follow-up: 1 months	10 (1 RCT)	⊕◯◯◯ Very low[a,b,e]	-	The mean pain catastrophising (PCS) was 12	MD 2.83 lower (11.58 lower to 5.92 higher)
Pain acceptance (CPAQ) follow-up: 1 months	10 (1 RCT)	⊕◯◯◯ Very low[a,b,f]	-	The mean pain acceptance (CPAQ) was 74	MD 8.67 higher (7.22 lower to 24.56 higher)
Depression follow-up: 1 months	22 (1 RCT)	⊕◯◯◯ Very lowa,b,g	-	The mean depression was 0	MD 0.27 lower (3 lower to 2.46 higher)
Sleep disturbance follow-up: 1 months	22 (1 RCT)	⊕⊕◯◯ Low[a,b,h]	-	The mean sleep disturbance was 55.92	MD 5.69 lower (13.47 lower to 2.09 higher)

a. 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

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

c. MIDs used to assess imprecision were ±0.63

d. MIDs used to assess imprecision were ±0.92

e. MIDs used to assess imprecision were ±4.77

f. MIDs used to assess imprecision were ±7.14

g. MIDs used to assess imprecision were ±2.16

h. MIDs used to assess imprecision were ±4.08

Hypnosis +mindfulness vs hypnosis alone

Table 23: Hypnosis +mindfulness vs hypnosis alone

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Hyp alone	Risk difference with Hyp +mindfulness
Average Pain Intensity (NRS 0-10, lower is better outcome) follow-up: 1 months	9 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	-	The mean average Pain Intensity (NRS 0-10, lower is better outcome) was 4.48	MD 1.17 lower (3.45 lower to 1.11 higher)
Pain interference (BPI, lower is better) follow-up: 1 months	9 (1 RCT)	⊕◯◯◯ Very low[a,b,d]	-	The mean pain interference (BPI, lower is better) was 4.69	MD 1.26 lower (4.09 lower to 1.57 higher)
Pain catastrophising (PCS) follow-up: 1 months	9 (1 RCT)	⊕◯◯◯ Very low[a,b,e]	-	The mean pain catastrophising (PCS) was 14.8	MD 2.8 lower (16.46 lower to 10.86 higher)
Pain acceptance (CPAQ) follow-up: 1 months	9 (1 RCT)	⊕◯◯◯ Very low[a,b,f]	-	The mean pain acceptance (CPAQ) was 72.4	MD 1.6 higher (15.23 lower to 18.43 higher)
Depression (PHQ-8) follow-up: 1 months	20 (1 RCT)	⊕◯◯◯ Very low[a,b,g]	-	The mean depression (PHQ-8) was 0	MD 1.1 lower (5.56 lower to 3.36 higher)
Sleep disturbance (SF-8) follow-up: 1 months	20 (1 RCT)	⊕◯◯◯ Very low[a,b,h]	-	The mean sleep disturbance (SF-8) was 52.84	MD 3.08 higher (6.81 lower to 12.97 higher)

a. 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

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

c. MIDs used to assess imprecision were ±0.73

d. MIDs used to assess imprecision were ±1.01

e. MIDs used to assess imprecision were ±5.88

f. MIDs used to assess imprecision were ±8.63

g. MIDs used to assess imprecision were ±2.35

h. MIDs used to assess imprecision were ±4.93

Self-hypnosis training compared to progressive muscle relaxation

Table 24: Clinical evidence summary: Self-hypnosis training compared to progressive muscle relaxation

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with progressive muscle relaxation	Risk difference with Self-hypnosis training
Pain intensity (NRS 0-10) follow-up: 3 months	23 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	-	The mean pain intensity (NRS 0-10) was 0	MD 0.13 higher (1.55 lower to 1.81 higher)
Pain interference (modified BPI) follow-up: 3 months	23 (1 RCT)	⊕◯◯◯ Very low[a,b,d]	-	The mean pain interference (modified BPI) was 0	MD 0.57 lower (3.02 lower to 1.88 higher)

a. 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

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

c. MIDs used to assess imprecision were ±0.68

d. MIDs used to assess imprecision were ±1.28

Mindfulness compared to control (waitlist) for pain in MS

Table 25: Clinical evidence summary: Mindfulness compared to control (waitlist)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control (waitlist)	Risk difference with Mindfulness
Distress (GHQ, lower is better outcome) follow-up: 3 months	40 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	-	The mean distress (GHQ, lower is better outcome) was 15.17	MD 5.24 lower (8.18 lower to 2.3 lower)
Depression (HADS) follow-up: 3 months	40 (1 RCT)	⊕◯◯◯ Very low[a,b,d]	-	The mean depression (HADS) was 7.28	MD 2.15 lower (4.53 lower to 0.23 higher)
HADS anxiety follow-up: 3 months	40 (1 RCT)	⊕◯◯◯ Very low[a,b,e]	-	The mean HADS anxiety was 7.37	MD 2.53 lower (4.76 lower to 0.3 lower)
MSIS Psychological follow-up: 3 months	40 (1 RCT)	⊕◯◯◯ Very low[a,b,f]	-	The mean MSIS Psychological was 7.42	MD 5.04 lower (9.3 lower to 0.78 lower)
MSIS-physical follow-up: 3 months	40 (1 RCT)	⊕◯◯◯ Very low[a,b,g]	-	The mean mSIS-physical was 65.57	MD 4.93 lower (17.28 lower to 7.42 higher)
Pain rating (NRS 0-10, lower is better outcome) follow-up: 3 months	40 (1 RCT)	⊕◯◯◯ Very low[a,b,h]	-	The mean pain rating (NRS 0-10, lower is better outcome) was 4.28	MD 2.55 lower (4.09 lower to 1.01 lower)
EQ5D follow-up: 3 months	40 (1 RCT)	⊕◯◯◯ Very low[a,b,i]	-	The mean EQ5D was 0.5	MD 0.01 higher (0.2 lower to 0.22 higher)

a. 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

b. 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

c. MIDs used to assess imprecision were ±4.39

d. MIDs used to assess imprecision were ±1.71

e. MIDs used to assess imprecision were ±1.7

f. MIDs used to assess imprecision were ±2.86

g. MIDs used to assess imprecision were ±9.52

h. MIDs used to assess imprecision were ±1.41

i. MIDs used to assess imprecision were ±0.18

CBT + standard care (CBT/SC) compared to MS education + standard care (ED/SC) for pain in MS

Table 26: Clinical evidence summary: CBT + standard care (CBT/SC) compared to MS education + standard care (ED/SC)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with MS education + standard care (ED/SC)	Risk difference with CBT + standard care(CBT/SC)
Pain severity follow-up: 15 weeks	20 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	-	The mean pain severity was 3.57	MD 0.21 higher (0.84 lower to 1.26 higher)
Pain interference (WHYMPI interference subscale) follow-up: 15 weeks	20 (1 RCT)	⊕⊕◯◯ Low[a,b,d]	-	The mean pain interference (WHYMPI interference subscale) was 3.96	MD 1.6 lower (2.81 lower to 0.39 lower)
Depression (Beck Depression Inventory) follow-up: 15 weeks	20 (1 RCT)	⊕◯◯◯ Very low[a,b,e]	-	The mean depression (Beck Depression Inventory) was 10.85	MD 2.49 lower (8.59 lower to 3.61 higher)

a. 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

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

c. MIDs used to assess imprecision were ±0.61

d. MIDs used to assess imprecision were ±0.56

e. MIDs used to assess imprecision were ±3.23

Transcutaneous Spinal Direct Current Stimulation (tsDCS) compared to sham

Table 27: Clinical evidence summary: Transcutaneous Spinal Direct Current Stimulation (tsDCS) compared to sham

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with sham	Risk difference with Transcutanious Spinal Direct Current Stimulation (tsDCS)
Neuropathic pain symptoms inventory (NPSI) follow-up: 1 months	33 (1 RCT)	⊕⊕◯◯ Low[a,b,c]	-	The mean neuropathic pain symptoms inventory (NPSI) was 33.7	MD 12.7 lower (22.17 lower to 3.23 lower)

a. 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

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

c. MIDs used to assess imprecision were ±9.82

Transcutaneous Direct Current Stimulation (tDCS) compared to sham

Table 28: Clinical evidence summary: Transcutaneous Direct Current Stimulation (tDCS) compared to sham

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Sham	Risk difference with tDCS
Pain (VAS) follow-up: 4 weeks	46 (2 RCTs)	⊕⊕⊕◯ Moderate[a,b]	-	The mean Pain VAS score in the sham group was 52.1 in n=1 study (scale 0-100) and 5.8 in n=1 study (scale unclear)	SMD 0.44 lower (1.03 lower to 0.15 higher)
Depression (DASS or HADS) follow-up: 4 weeks	46 (2 RCTs)	⊕⊕◯◯ Low[a,c]	-	The mean depression score in the sham group was 6.3 in n=1 study (HADS scale, usually 0-21) and 12.8 in n=1 study (DASS scale, scale usually 0-42)	SMD 0.41 SD lower (0.99 lower to 0.18 higher)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Sham	Risk difference with tDCS
Anxiety (DASS or HADS) follow-up: 4 weeks	46 (2 RCTs)	⊕⊕◯◯ Low[a,d]	-	The mean depression score in the sham group was 8.1 in n=1 study (HADS scale, usually 0-21) and 12.1 in n=1 study (DASS scale, scale usually 0-42)	SMD 0.4 SD lower (0.98 lower to 0.19 higher)
MSQOL-54 Physical follow-up: 4 weeks	30 (1 RCT)	⊕◯◯◯ Very low[a,e,f]	-	The mean MSQOL-54 Physical was 39.6	MD 12.9 higher (0.34 lower to 26.14 higher)
MSQOL-54 Mental follow-up: 4 weeks	30 (1 RCT)	⊕⊕◯◯ Low[a,g]	-	The mean MSQOL-54 Mental was 12.5	MD 57.7 higher (48.37 higher to 67.03 higher)
Pain (NPS) follow-up: 4 weeks	30 (1 RCT)	⊕◯◯◯ Very low[a,h]	-	The mean pain (NPS) was 44.6	MD 5.7 lower (22.89 lower to 11.49 higher)

a. 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

b. MIDs used to assess imprecision were ±5.3

c. MIDs used to assess imprecision were ±2.7

d. MIDs used to assess imprecision were ±2.6

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

f. MIDs used to assess imprecision were ±9.25

g. MIDs used to assess imprecision were ±9.75

h. MIDs used to assess imprecision were ±8.25

A study by Mori 2010[23] which was included in the previous guideline compared Anodal transcranial direct current stimulation with sham transcranial direct current stimulation. VAS pain intensity data were presented and were reported in forest plots; the other outcome measures

were only shown graphically. On the Short Form McGill Questionnaire and the Multiple Sclerosis Quality of Life-54, the authors reported that scores were reduced in the active group compared with the control group after the first week and this effect persisted until the last evaluation. There were no effects of treatment on the Beck Depression Inventory or VAS for anxiety [High risk of bias for methodological limitations].

Transcutaneous Random Noise Stimulation (tRNS)

Table 29: Clinical evidence summary for transcutaneous Random Noise Stimulation (tRNS) compared to sham

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with sham	Risk difference with tRNS
VAS (0-100) follow-up: 4 weeks	16 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	-	The mean VAS (0-100) was 50.3	MD 3.1 lower (21 lower to 14.8 higher)
Brief Pain Inventory (Global score) follow-up: 4 weeks	16 (1 RCT)	⨁◯◯◯ Very low[a, b,,d]	-	The mean brief Pain Inventory (Global score) was 9.2	MD 0.6 lower (3.64 lower to 2.44 higher)

a. 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

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

c. MIDs used to assess imprecision were ±10.52

d. MIDs used to assess imprecision were ±1.47

Transcutaneous Electrical Nerve Stimulation (TENS) compared to Placebo

Al-Smadi 2003[1] was included in the previous guideline and is a pilot study into the use of TENS (group 1: low frequency TENS (4Hz, 200μs) or group 2: high frequency TENS (110Hz, 200μs) versus placebo TENS; each was applied by a researcher for 45 minutes 3 times a week for 6 weeks. The study was underpowered as there were only 5 patients in each group. Not all baseline data were shown, but of those that were

shown, there were significant differences between the groups at baseline. The authors narratively report no significant differences between the groups on any outcome measure (VAS, right/leg pain, Leeds Multiple Sclerosis Quality of Life questionnaire, Roland Morris Disability Questionnaire, McGill Pain Questionnaire, SF-36 physical and mental) [High risk of bias for methodological limitations]

Warke 2006[34] is an extension of Warke 2004[35] which was included in the previous guideline. Ninety patients were equally randomised into 3 groups: group 1: low frequency TENS (4Hz, 200μs) or group 2: high frequency TENS (110Hz, 200μs) versus placebo TENS. Participants self-applied TENS for 45 minutes twice a day for 6 weeks and at any time a painful episode occurred. The authors narratively report no significant differences between the groups on any outcome measure or within groups over time (McGill Pain Questionnaire pain rating and affective sub-scale, VAS, Barthel Index, Leeds Multiple Sclerosis Quality of Life Questionnaire, SF-36 physical and mental) [High risk of bias for methodological limitations].

Hydrotherapy (Ai-chi) compared to control

A study by Castro-Sanchez 2012[7] compared Ai-Chi exercise in a swimming pool to breathing and contraction-relaxation exercises in a therapy room was included in the previous guideline. Outcomes were presented as medians and standard deviations rather than as means and standard deviations making the data unsuitable for RevMan analysis. Therefore, a full GRADE rating could not be obtained and only risk of bias was assessed (see table below). The authors report that the intervention group showed a significant and clinically relevant decrease in pain intensity versus baseline, with a reduction of 50% in Pain on a VAS in the Ai-chi group compared to 23% reduction in the control group at 20 weeks. Significant improvements were observed in both groups in the MSIS psychological subscale compared to baseline (within groups) as well as a significant improvement in the intervention group compared to the control (between groups). However, only the intervention group showed a significant reduction in the physical subscale at week 20 compared to baseline. The Ai-chi group also showed a significant improvement in depression symptoms on the Beck Depression inventory from baseline (52%) compared to the control group.

	Allocation	Baseline Median (SD)	Week 20 Median (SD)	Week 30 Median (SD)	Risk of Bias
Pain VAS	Control	7 (1.9)	6 (2.3)	6 (2.4)	High
	Ai-Chi	7 (2.1)	3 (2.3)*, #	5 (2.5)*	
MSIS- Physical	Control	46 (18.34)	45 (17.14)	46 (15.93)	High
	Ai-Chi	48 (15.91)	41 (12.37)*, #	48 (12.89)*, #	
MSIS-psychological	Control	30 (23.53)	25 (19.36)*	29 (20.39)	High
	Ai-Chi	34 (29.47)	21 (15.73)*, #	24 (11.27)*, #	

	Allocation	Baseline Median (SD)	Week 20 Median (SD)	Week 30 Median (SD)	Risk of Bias
Beck Depression Inventory II	Control	15 (8.68)	13 (5.91)	14 (8.93)	High
	Ai-Chi	14 (7.72)	5 (3.2)*,#	11 (5.92)	

Median (SD), * significant change from baseline value within group. # Significant difference between experimental and control group

1.1.7 Economic evidence

1.1.7.1 Included studies

No health economic studies were included.

1.1.7.2 Excluded studies

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

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

1.1.8 Economic model

This area was not prioritised for new cost-effectiveness analysis.

1.1.9 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Resource	Unit cost per working hour (a)
Hospital-based staff	
Consultant: Medical	£148
Consultant: psychiatric	£146
Clinical psychologist (band 8a)	£72
Hospital physiotherapist (band 7)	£62
Hospital occupational therapist (band 7)	£62
Clinical Nurse specialist (band 7)	£62
Community-based staff	
Physiotherapy (band 7)	£60
Occupational therapy (band 7)	£60
Clinical psychologist, Counsellor (specialist) (band 7)	£60
Nurse (GP practice)	£41
Interventions	
Cognitive behavioural therapy (CBT) per session	£106 (b)
Mindfulness-based cognitive therapy – group-based intervention	£91 per hour of direct contact £181 per session, £16 per service user (c)
Transcranial magnetic stimulation procedure cost (excluding machine)	£259 (d)
Other	
TENS machine (provided on loan)	£17.40-£31.10 (e)

Source: PSSRU 2020[10]

(a) Qualification costs included (excluding individual and productivity costs)

(b) Taken from PSSRU (2017)[9] and inflated to 2018/19 prices using OECD purchasing power parities (PPPs)[30]

(c) Taken from PSSRU (2013)[8] and inflated to 2018/2019 prices using OECD purchasing power parities (PPPs)[30]

(d) NHS reference costs 2018-2019[28], HRG AA57 (Minimal Intracranial Procedures, 19 years and over, outpatient procedure), which covers OPCS-4 code A09.8 Other specified neurostimulation of brain. This is the cost of the procedure only (such as staff time), does not include the cost of the machine if this is a high-cost device.

(e) NHS supply chain catalogue (May 2021)[29]: TENS machine TPN 200 Plus (NPC: EAZ359) and Dual channel TENS machine (NPC: EAZ421)

1.1.10 Evidence statements

Effectiveness/Qualitative

- See GRADE tables in Appendix F.

Economic

- No relevant economic evaluations were identified.

1.1.11 The committee's discussion and interpretation of the evidence

1.1.11.1. The outcomes that matter most

The committee considered all outcomes listed in the protocol to be critical and of equal importance in decision-making. These outcomes were pain intensity using validated pain scales such as the Visual Analogue Scale (VAS) and Numerical Rating Scale (NRS), pain reduction for example >30% and 50% pain reduction from baseline, patient-reported outcome measures for quality of life such as Multiple Sclerosis Quality of Life Inventory (MSQLI), EQ5D and SF-36, adverse events of treatment, Expanded Disability Status Scale (EDSS), MS Functional Composite or its subscales if not reported (MSFC), mood related outcomes for example validated depression scales and anxiety scales, and changes in sleep quality, sleep related impairments and sleep disturbance.

Outcomes assessing pain, anxiety, depression and quality of life were generally well reported and available for most comparisons. Most of the studies reported at least one outcome on pain and one on mood changes or quality of life. However, the measurement, scales and reporting differed across the studies which precluded pooling of the data. Sleep disturbances were less commonly reported and outcomes on adverse events of treatments were not included in any of the studies.

There were no relevant randomised or non-randomised trials on multidisciplinary rehabilitation programmes, lycra garments, acupuncture or Transcranial Magnetic Stimulation (TMS).

1.1.11.2 The quality of the evidence

Twenty-four studies were included in this review, 6 of which were included in the previous guideline. Twenty-one of these were parallel randomised controlled trials, 2 were randomised cross-over trials and 1 was a mixed methods (qualitative and quantitative) study. No relevant non-randomised controlled trials were identified.

The included studies were small with participant numbers ranging from 15 to 163. Some were feasibility or pilot studies which did not explicitly report power calculations and were likely to be underpowered.

Pooling of the data was not possible due to different interventions used in specific programs or context, different comparators, and different outcomes. This resulted in many different comparisons and outcomes data only from single small studies.

The quality of the evidence for outcomes as assessed by GRADE was either low or very low. Downgrading was mainly due to risk of bias or imprecision. Risk of bias was most commonly due to concerns about allocation concealment, the randomisation process and lack of blinding especially in view of the outcomes being subjective. There was much uncertainty in the size and direction of effect for most outcomes leading to the evidence being downgrading for imprecision. There were no concerns about indirectness of the populations, interventions or outcomes.

1.1.11.3 Benefits and harms

As the studies varied widely in terms of interventions and reporting of outcomes, the majority of the data could not be pooled. This meant that the evidence was sparse and mostly from small single studies. Based on the point estimate, there seemed to be a possible clinically important benefit for interventions such as yoga, relaxation, massage, mindfulness, reflexology, CBT and Transcutaneous Direct Current Stimulation (tDCS) compared to control as well as hypnosis with neurofeedback compared to hypnosis alone particularly on reducing pain and improving psychological outcomes. However, the confidence intervals around these point estimates were quite wide and could also be consistent with no difference and/or worse

scores in the intervention compared to control. Therefore, the committee did not have high confidence in the available evidence and could not make strong conclusions.

Due to the limitations of the evidence, the committee could not make any recommendations for or against using any particular non-pharmacological intervention for people with MS. However, the committee acknowledged that in many people with MS the cause of pain may not always be due to MS but rather to other comorbid or underlying conditions. Therefore, patients would benefit from individual review by healthcare professionals to investigate the cause of pain and establish a diagnosis first so that treatment specific to the cause of pain can be offered. They agreed that determining the cause of pain, will prevent unnecessary treatment and possible side effects, and ensure pain is managed correctly. In addition, being aware of the impact of pain on MS patients and reducing it is likely to improve a person's quality of life, health and physical and mental well-being.

The committee noted that although the evidence for clinical benefit of interventions that increased physical activity or involved stretching such as yoga wasn't strong, it was in line with their clinical experience. These exercises can be therapeutic and help people with MS cope better with their pain. They highlighted this by amending a previous recommendation [1.5.30] to include immobility as a potential cause of musculoskeletal pain. In addition, clinicians should be aware that spasticity may also be a primary contributor to pain in MS. A recommendation for these types of exercise in MS for pain was not made given there was limited evidence and there could be a resource impact.

The majority of the evidence for mood related outcomes such as anxiety and depression showed some benefit when a non-pharmacological intervention was used. Although this was not always clinically important, the committee acknowledged the impact of pain on the mental wellbeing of people with MS. Pain can significantly reduce mobility and limit activities of daily living. This in turn can lead to low mood and often affects the person's ability to deal with pain. Therefore, the committee made recommendation to bring awareness to this fact and to the existence of NICE guidelines on depression in adults with chronic physical problems.

Although evidence was not formally reviewed for the pharmacological management of pain in MS as this not prioritised for inclusion in this guideline, the committee were aware that there is existing NICE guidance on the pharmacological management of neuropathic pain which is relevant to people with MS. Due to its limited success and side effects non-pharmacological interventions were the focus of this review.

There is still a lack of evidence in the area and the committee felt that further research should be conducted to reduce the existing uncertainty regarding the effectiveness of non-pharmacological interventions for pain. Therefore, a recommendation for further research was made in the hope that more robust research would support decision making in the development of future recommendations.

1.1.11.4 Cost effectiveness and resource use

No health economic evidence was identified for this review. Unit costs were provided to aid consideration of cost effectiveness. These included the unit cost of various health care professionals who may provide interventions for non-pharmacological management of pain. In addition, the published unit cost of various interventions was presented: cognitive behavioural therapy, mindfulness, transcranial magnetic stimulation (TMS) and the cost of hiring a TENS machine. The committee noted that the unit cost of TMS (£259) represents the reference cost for TMS for the treatment of depression. The guideline specialist co-optee noted that only one centre nationally offers TMS for treating pain and that it costs approximately £400.

Due to the limited clinical evidence and lack of cost-effectiveness evidence, the committee did not make specific intervention recommendations, but instead chose to continue to cross reference to the NICE neuropathic pain guidelines.

The committee did make a new recommendation to assess and, where appropriate, investigate the cause of pain. The committee noted that this assessment could be done by many different healthcare professionals such as a rehabilitation physician, a physiotherapist, a GP, a neurologist, or an MS nurse. They discussed that this would usually involve history taking and for some may require further investigation such as scans. The aim of this assessment is to eliminate other causes of pain such as cancer for example. It was noted that although there may be costs associated with further investigations such as scans, it was agreed that these are likely to be offset by identifying the cause of pain and therefore offering more appropriate treatment. The committee agreed that assessing and investigating the cause of pain is part of current best practice and it is not expected to lead to a significant resource impact.

1.1.11.5 Other factors the committee took into account

The committee were aware of the NICE guideline on Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain (NG193).

The committee supported the development of a core outcome set for multiple sclerosis to facilitate the pooling of studies.

1.1.12 Recommendations supported by this evidence review

This evidence review supports recommendations 1.5.34 to 1.5.37 and the research recommendation on pain.

1.1.13 References

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Appendices

Appendix A – Review protocols

Review protocol for non-pharmacological management of pain in MS

ID	Field	Content
0.	PROSPERO registration number	CRD42021261262
1.	Review title	Non-pharmacological management of pain
2.	Review question	For adults with MS, including people receiving palliative care, what is the clinical and cost effectiveness of **non-pharmacological** interventions for pain?
3.	Objective	To determine the clinical effectiveness of non-pharmacological interventions in people with multiple sclerosis (MS).
4.	Searches	Key papers: • Lancet Neurol. 2015 Feb;14(2):194-207. doi: 10.1016/S1474-4422(14)70231-5. Treatment of Progressive Multiple Sclerosis: What Works, What Does Not, and What Is Needed. Anthony Feinstein, Jenny Freeman, Albert C Lo. PMID: 25772898 DOI: 10.1016/S1474-4422(14)70231-5 • Cochrane review (Amatya 2018): Non-pharmacological interventions for chronic pain in multiple sclerosis https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012622.pub2/full • Sawant A, Dadurka K, Overend T, Kremenchutzky M: Systematic review of efficacy of TENS for management of central pain in people with multiple sclerosis. Multiple Sclerosis and Related Disorders 2015, 4(3):219-227. • Jawahar R, Oh U, Yang S, Lapane KL: Alternative approach: a systematic review of non-pharmacological non-spastic and non-trigeminal pain

		management in multiple sclerosis. European journal of physical and rehabilitation medicine 2014, 50(5):567-577. The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos • Date limitations – 2014 onwards (date of CG 186 publications) • English language studies • Human studies The searches may be re-run 6 weeks before the final committee meeting, and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Multiple sclerosis
6.	Population	Inclusion: Adults (≥18 years) with MS, including people receiving palliative care. Exclusion: Children and young people <18 years).

7.	Intervention	Any non-pharmacological intervention, for example: • Multidisciplinary rehabilitation/programmes • Acupuncture • Self-management programmes • Exercise (for example stretching, standing, splinting, gym prescription, yoga, tai chi, pilates, relaxation) • Lycra garments • Transcutaneous electrical nerve stimulation (TENS) • Psychological based therapies: CBT, hypnosis, • Mindfulness • Hydrotherapy • Complementary therapies (e.g., massage) • TMS (transcranial magnetic stimulation)
8.	Comparator	Interventions will be compared to each other, placebo, sham, no treatment or usual care.
9.	Types of study to be included	Systematic reviews of RCTs and RCTs will be considered for inclusion. Cross-over trials will also be considered for inclusion If there insufficient RCT evidence, non-randomised cohort studies will be considered provided they have adjusted for the following variables: - age - fatigue - depression - anxiety - gender Published NMAs and IPDs will be considered for inclusion. Studies with mixed populations for example MS patients and spinal cord injury patients will also be considered if there are at least 60% MS patients. If insufficient evidence available, studies with <60% may be included but downgraded for indirectness.
10.	Other exclusion criteria	Non-English language studies.

		. Conference abstracts will be excluded because they are unlikely to contain enough information to assess whether the population matches the review question in terms of previous medication use, or enough detail on outcome definitions, or on the methodology to assess the risk of bias of the study.
11.	Context	CG 186 did not make any recommendations on non-pharmacological management of pain but cross refers to CG 173 pharmacological management of neuropathic pain: 1.5.29 Treat neuropathic pain in people with MS according to the NICE guideline on neuropathic pain in adults and refer to pain services if appropriate. 1.5.30 Be aware that musculoskeletal pain is common in people with MS and is usually secondary to problems with mobility and posture. Assess musculoskeletal pain, offer treatment to the person and refer them as appropriate. The guideline will also refer to the NICE Cannabis based medicinal products guideline (NG 144)
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical. • Pain intensity using validated pain scales for example Visual Analogue Scale and numerical rating scale • Pain reduction for example >30% and 50% pain reduction from baseline • Patient-reported outcome measures, which refer generally to quality of life and the scales of Multiple Sclerosis Quality of Life Inventory (MSQLI); life satisfaction, EQ5D, SF-36 • Adverse effects of treatment.

		• Adverse events leading to withdrawal or lack of efficacy • Expanded Disability Status Scale (EDSS) • MS Functional Composite or its subscales if not reported (MSFC). • Functional improvement • Reduction of care • Mood related outcomes for example validated depression scales and anxiety scales • Changes in sleep quality/sleep related impairments/ sleep disturbance Follow up: • 3 months up to 6 months (less months may be included in view of palliative care subgroup) • If studies only report > 6 months, these may be included and downgraded for indirectness.
13.	Secondary outcomes (important outcomes)	n/a
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 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. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately

		• a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments 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. 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 appropriate checklist as described in Developing NICE guidelines: the manual. The following checklist will be used according to study design being assessed: • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • Non randomised studies, including cohort studies: Cochrane ROBINS-I
16.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. To maximise the amount of data for meta-analysis, where multiple scales have been used for an outcome such as mobility, fatigue or spasticity, the most commonly reported ones across studies will be extracted and meta-analysed with priority given to those included in CG 186. Where available, outcome data from new studies will be meta-analysed with corresponding data included in CG 186.

		Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. 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. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ Where meta-analysis is not possible, data will be presented, and quality assessed individually per outcome. If sufficient data is available, meta-regression or NMA-meta-regression will be conducted. WinBUGS will be used for network meta-analysis, if possible, given the data identified.	
17.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: • According to type (for example relapsing remitting MS, secondary progressive MS, and primary progressive MS) • According to disability (for example based on EDSS scores) • Disease modifying treatment status (currently using and not currently using) or other treatments for comorbidities • Type of pain (neuropathic, central, headache, trigeminal neuralgia).	
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	October 2020	
22.	Anticipated completion date	July 2022	
23.	Stage of review at time of this submission	Review stage	Started / Completed
		Preliminary searches	☐ / ☐
		Piloting of the study selection process	☐ / ☐
		Formal screening of search results against eligibility criteria	☐ / ☐
		Data extraction	☐ / ☐
		Risk of bias (quality) assessment	☐ / ☐
		Data analysis	☐ / ☐
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail MultipleSclerosisUpdate@nice.org.uk	

		5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre
25.	Review team members	From the National Guideline Centre: Dr Sharon Swain [Guideline lead] Dr Saoussen Ftouh [Senior systematic reviewer] Nicole Downes [Systematic reviewer] Sophia Kemmis Betty [Senior health economist] Claire Sloane [Health economist] Lina Gulhane [Information specialist] Emma Clegg [Information specialist] Kate Ashmore [Project Manager]
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.

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

Table 30: 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. For questions being updated, the search will be run from 2014, which was the cut-off date for the searches conducted for NICE guideline CG186.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2005, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2005 that were included in the previous guideline will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. 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).[24] **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 2005 or later (including any such studies included in the previous guideline) but that depend on unit costs and resource data entirely or predominantly from before 2005 will be rated as 'Not applicable'. • Studies published before 2005 (including any such studies included in the previous guideline) 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

This literature search strategy was used for the following review:

- The clinical and cost effectiveness of non-pharmacological interventions for pain for adults with MS, including people receiving palliative care.

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[24]

For more information, please see the Methodology review 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.

Table 31: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	01 January 2014 – 08 September 2021	Randomised controlled trials Systematic review studies Exclusions (animal studies, letters, comments, children)
Embase (OVID)	01 January 2014 – 08 September 2021	Randomised controlled trials Systematic review studies Exclusions (animal studies, letters, comments, conference abstracts, children)
The Cochrane Library (Wiley)	Cochrane Reviews 2014 to 2021 Issue 9 of 12 CENTRAL 2014 to 2021 Issue 9 of 12	None Exclusions (conference abstracts & clinical trials)
Epistemonikos (The Epistemonikos Foundation)	01 January 2014 – 08 September 2021	Systematic Reviews Exclusions (Cochrane Reviews)

Medline (Ovid) search terms

1.	exp Multiple Sclerosis/
2.	((multiple or disseminated) adj2 scleros*).ti,ab.
3.	encephalomyelitis disseminata.ti,ab.
4.	MS.ti.
5.	Myelitis, Transverse/
6.	transverse myelitis.ti,ab.
7.	or/1-6
8.	letter/
9.	editorial/

10.	news/
11.	exp historical article/
12.	Anecdotes as Topic/
13.	comment/
14.	case report/
15.	(letter or comment*).ti.
16.	or/8-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animals/ not humans/
20.	exp Animals, Laboratory/
21.	exp Animal Experimentation/
22.	exp Models, Animal/
23.	exp Rodentia/
24.	(rat or rats or rodent* or mouse or mice).ti.
25.	or/18-24
26.	7 not 25
27.	limit 26 to English language
28.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
29.	27 not 28
30.	exp Pain/
31.	(pain* or neuralgia or nociceptor* or ache or aching or twinge* or pang* or spasm* or cramp* or sore*).ti,ab.
32.	((physical or nerve* or muscl*) adj2 (suffering or hurt* or discomfort* or uncomfort*)).ti,ab.
33.	or/30-32
34.	29 and 33
35.	randomized controlled trial.pt.
36.	controlled clinical trial.pt.
37.	randomi#ed.ti,ab.
38.	placebo.ab.
39.	randomly.ti,ab.
40.	Clinical Trials as topic.sh.
41.	trial.ti.
42.	or/35-41
43.	Meta-Analysis/
44.	exp Meta-Analysis as Topic/
45.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
46.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
47.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
48.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
49.	(search* adj4 literature).ab.
50.	(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.

51.	cochrane.jw.
52.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
53.	or/43-52
54.	34 and (42 or 53)

1 **Embase (Ovid) search terms**

1.	exp *Multiple Sclerosis/
2.	((multiple or disseminated) adj2 scleros*).ti,ab.
3.	encephalomyelitis disseminata.ti,ab.
4.	MS.ti.
5.	myelitis/
6.	transverse myelitis.ti,ab.
7.	or/1-6
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.
11.	(conference abstract or conference paper).pt.
12.	case report/ or case study/
13.	(letter or comment*).ti.
14.	or/8-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animal/ not human/
18.	nonhuman/
19.	exp Animal Experiment/
20.	exp Experimental Animal/
21.	animal model/
22.	exp Rodent/
23.	(rat or rats or rodent* or mouse or mice).ti.
24.	or/16-23
25.	7 not 24
26.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
27.	25 not 26
28.	limit 27 to English language
29.	exp pain/
30.	(pain* or neuralgia or nociceptor* or ache or aching or twinge* or pang* or spasm* or cramp* or sore*).ti,ab.
31.	((physical or nerve* or muscl*) adj2 (suffering or hurt* or discomfort* or uncomfort*)).ti,ab.
32.	or/29-31
33.	28 and 32
34.	random*.ti,ab.
35.	factorial*.ti,ab.
36.	(crossover* or cross over*).ti,ab.
37.	((doubl* or singl*) adj blind*).ti,ab.
38.	(assign* or allocat* or volunteer* or placebo*).ti,ab.

39.	crossover procedure/
40.	single blind procedure/
41.	randomized controlled trial/
42.	double blind procedure/
43.	or/34-42
44.	systematic review/
45.	meta-analysis/
46.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
47.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
48.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
49.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
50.	(search* adj4 literature).ab.
51.	(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.
52.	cochrane.jw.
53.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
54.	or/44-53
55.	33 and (43 or 54)

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

#1.	MeSH descriptor: [Multiple Sclerosis] explode all trees
#2.	((multiple or disseminated) NEAR/2 scleros*):ti,ab
#3.	encephalomyelitis disseminata:ti,ab
#4.	MS:ti
#5.	MeSH descriptor: [Myelitis, Transverse] this term only
#6.	transverse myelitis:ti,ab
#7.	(OR #1-#6)
#8.	MeSH descriptor: [Pain] explode all trees
#9.	(pain* or neuralgia or nociceptor* or ache or aching or twinge* or pang* or spasm* or cramp* or sore*):ti,ab
#10.	((physical or nerve* or muscl*) NEAR/2 (suffering or hurt* or discomfort* or uncomfort*)):ti,ab
#11.	(OR #8-#10)
#12.	#7 AND #11
#13.	conference:pt or (clinicaltrials or trialsearch):so
#14.	#12 NOT #13

2 **Epistemonikos search terms**

1.	((advanced_title_en:(Multiple sclerosis) OR advanced_abstract_en:(Multiple sclerosis)) AND (advanced_title_en:(pain* OR neuralgia OR nociceptor* OR ache OR aching OR twinge* OR pang* OR spasm* OR cramp* OR sore* OR discomfort* OR suffer* OR uncomfort* OR hurt*) OR advanced_abstract_en:(pain* OR neuralgia OR nociceptor* OR ache OR aching OR twinge* OR pang* OR spasm* OR cramp* OR sore* OR discomfort* OR suffer* OR uncomfort* OR hurt*))

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search with the Multiple Sclerosis population. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics. Searches for quality-of-life studies were run for general information.

Table 32: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	01 January 2014 – 07 September 2021	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, children)
Embase	01 January 2014 – 07 September 2021	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, conference abstracts, children)
Centre for Research and Dissemination (CRD)	HTA – 01 January 2014 – 31 March 2018 NHSEED – 01 January 2014 – March 2015	None
The International Network of Agencies for Health Technology Assessment (INAHTA)	01 January 2018 – 07 September 2021	None

Medline (Ovid) search terms

1.	exp Multiple Sclerosis/
2.	((multiple or disseminated) adj2 scleros*).ti,ab.
3.	encephalomyelitis disseminata.ti,ab.
4.	MS.ti.
5.	Myelitis, Transverse/
6.	transverse myelitis.ti,ab.
7.	or/1-6
8.	*Demyelinating Diseases/
9.	*Demyelinating Autoimmune Diseases, CNS/
10.	(Demyelinat* adj2 (syndrome* or disease* or autoimmun*)).ti,ab.
11.	(Chronic Cerebrospinal Venous Insufficiency or CCSVI).ti,ab.
12.	Venous Insufficiency/cf, co, di, dg, et [Cerebrospinal Fluid, Complications, Diagnosis, Diagnostic Imaging, Etiology]
13.	(Devic* adj (disease or syndrome)).ti,ab.
14.	((clinical* isolat* or radiological* isolat*) adj2 syndrome*).ti,ab.
15.	exp Optic Neuritis/

16.	((neuromyelitis or neuritis or neuropapillitis) adj2 (retrobulbar or optic*)).ti,ab.
17.	(NMO or NMOSD).ti,ab.
18.	or/1-17
19.	letter/
20.	editorial/
21.	news/
22.	exp historical article/
23.	Anecdotes as Topic/
24.	comment/
25.	case report/
26.	(letter or comment*).ti.
27.	or/19-26
28.	randomized controlled trial/ or random*.ti,ab.
29.	27 not 28
30.	animals/ not humans/
31.	exp Animals, Laboratory/
32.	exp Animal Experimentation/
33.	exp Models, Animal/
34.	exp Rodentia/
35.	(rat or rats or rodent* or mouse or mice).ti.
36.	or/29-35
37.	18 not 36
38.	limit 37 to English language
39.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
40.	38 not 39
41.	Economics/
42.	Value of life/
43.	exp "Costs and Cost Analysis"/
44.	exp Economics, Hospital/
45.	exp Economics, Medical/
46.	Economics, Nursing/
47.	Economics, Pharmaceutical/
48.	exp "Fees and Charges"/
49.	exp Budgets/
50.	budget*.ti,ab.
51.	cost*.ti.
52.	(economic* or pharmaco?economic*).ti.
53.	(price* or pricing*).ti,ab.
54.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.

55.	(financ* or fee or fees).ti,ab.
56.	(value adj2 (money or monetary)).ti,ab.
57.	or/41-56
58.	quality-adjusted life years/
59.	sickness impact profile/
60.	(quality adj2 (wellbeing or well being)).ti,ab.
61.	sickness impact profile.ti,ab.
62.	disability adjusted life.ti,ab.
63.	(qal* or qtime* or qwb* or daly*).ti,ab.
64.	(euroqol* or eq5d* or eq 5*).ti,ab.
65.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
66.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
67.	(hui or hui1 or hui2 or hui3).ti,ab.
68.	(health* year* equivalent* or hye or hyes).ti,ab.
69.	discrete choice*.ti,ab.
70.	rosser.ti,ab.
71.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
72.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
73.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
74.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
75.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
76.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
77.	or/58-76
78.	40 and 57
79.	40 and 77
80.	78 or 79

1 Embase (Ovid) search terms

1.	exp Multiple Sclerosis/
2.	((multiple or disseminated) adj2 scleros*).ti,ab.
3.	encephalomyelitis disseminata.ti,ab.
4.	MS.ti.
5.	myelitis/
6.	transverse myelitis.ti,ab.
7.	or/1-6
8.	demyelinating disease/
9.	(Demyelinat* adj2 (syndrome* or disease* or autoimmun*)).ti,ab.
10.	(Chronic Cerebrospinal Venous Insufficiency or CCSVI).ti,ab.
11.	vein insufficiency/co, di, et [Complication, Diagnosis, Etiology]
12.	(Devic* adj (disease or syndrome)).ti,ab.
13.	((clinical* isolat* or radiological* isolat*) adj2 syndrome*).ti,ab.

14.	exp optic neuritis/
15.	((neuromyelitis or neuritis or neuropapillitis) adj2 (retrobulbar or optic*)).ti,ab.
16.	(NMO or NMOSD).ti,ab.
17.	or/1-16
18.	letter.pt. or letter/
19.	note.pt.
20.	editorial.pt.
21.	(conference abstract or conference paper).pt.
22.	case report/ or case study/
23.	(letter or comment*).ti.
24.	or/18-23
25.	randomized controlled trial/ or random*.ti,ab.
26.	24 not 25
27.	animal/ not human/
28.	nonhuman/
29.	exp Animal Experiment/
30.	exp Experimental Animal/
31.	animal model/
32.	exp Rodent/
33.	(rat or rats or rodent* or mouse or mice).ti.
34.	or/26-33
35.	17 not 34
36.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
37.	35 not 36
38.	limit 37 to English language
39.	health economics/
40.	exp economic evaluation/
41.	exp health care cost/
42.	exp fee/
43.	budget/
44.	funding/
45.	budget*.ti,ab.
46.	cost*.ti.
47.	(economic* or pharmaco?economic*).ti.
48.	(price* or pricing*).ti,ab.
49.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
50.	(financ* or fee or fees).ti,ab.
51.	(value adj2 (money or monetary)).ti,ab.
52.	or/39-51
53.	quality adjusted life year/
54.	"quality of life index"/
55.	short form 12/ or short form 20/ or short form 36/ or short form 8/
56.	sickness impact profile/
57.	(quality adj2 (wellbeing or well being)).ti,ab.

58.	sickness impact profile.ti,ab.
59.	disability adjusted life.ti,ab.
60.	(qal* or qtime* or qwb* or daly*).ti,ab.
61.	(euroqol* or eq5d* or eq 5*).ti,ab.
62.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
63.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
64.	(hui or hui1 or hui2 or hui3).ti,ab.
65.	(health* year* equivalent* or hye or hyes).ti,ab.
66.	discrete choice*.ti,ab.
67.	rosser.ti,ab.
68.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
69.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
70.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
71.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
72.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
73.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
74.	or/53-73
75.	38 and 52
76.	38 and 74
77.	75 or 76

1 **NHS EED and HTA (CRD) search terms**

#1.	MeSH DESCRIPTOR Multiple Sclerosis EXPLODE ALL TREES
#2.	(((multiple or disseminated) adj2 scleros*))
#3.	(encephalomyelitis disseminata)
#4.	(MS)
#5.	MeSH DESCRIPTOR Myelitis, Transverse EXPLODE ALL TREES
#6.	(transverse myelitis)
#7.	MeSH DESCRIPTOR Demyelinating Diseases EXPLODE ALL TREES
#8.	((Demyelinat* adj2 (syndrome or disease)))
#9.	(Chronic Cerebrospinal Venous Insufficiency)
#10.	MeSH DESCRIPTOR Venous Insufficiency
#11.	(((Devic or "devic's") adj (disease or syndrome)))
#12.	(((clinically isolated or radiologically isolated) adj syndrome))
#13.	MeSH DESCRIPTOR Optic Neuritis EXPLODE ALL TREES
#14.	(Neuromyelitis Optica)
#15.	#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

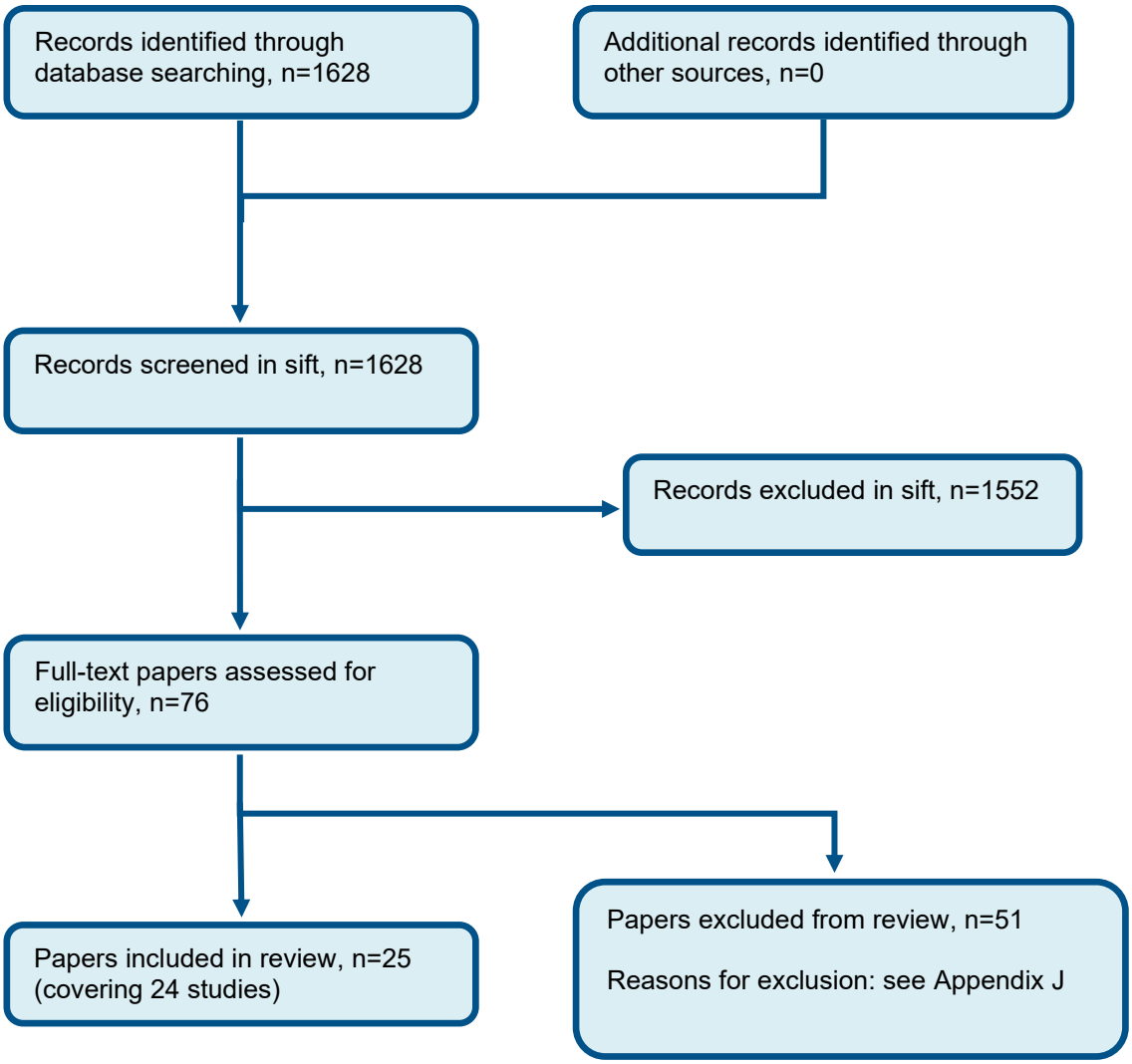
2 **INAHTA search terms**

1.	(multiple sclerosis)[mh] OR (((multiple or disseminated) adj2 scleros*)) OR (encephalomyelitis disseminata) OR (MS)[Title] OR (Myelitis, Transverse)[mh] OR (transverse myelitis) OR (Demyelinating Diseases)[mh] OR (Demyelinating Autoimmune Diseases, CNS)[mh] OR ((Demyelinat* adj2 (syndrome* or disease* or autoimmun*))) OR ((Chronic Cerebrospinal Venous Insufficiency or CCSVI)) OR (venous insufficiency)[mh] OR ((Devic* adj (disease or syndrome))) OR (((clinical* isolat* or radiological* isolat*) adj2 syndrome*)) OR (optic neuritis)[mh] OR (((neuromyelitis or neuritis or neuropapillitis) adj2 (retrobulbar or optic*))) OR ((NMO or NMOSD))

3

Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of non-pharmacological management of pain in MS



Appendix D – Effectiveness evidence

D.1 Studies extracted using EPPI reviewer (new studies identified in current update)

Alschuler, 2021

Bibliographic Reference	Alschuler, K. N.; Altman, J. K.; Ehde, D. M.; Feasibility and acceptability of a single-session, videoconference-delivered group intervention for pain in multiple sclerosis; Rehabilitation Psychology; 2021; vol. 66 (no. 1); 22-30

Study details

Trial name / registration number	
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	Home based
Study dates	
Sources of funding	National Multiple Sclerosis Society
Inclusion criteria	(a) MS diagnosis using revised McDonald Criteria in the past 36 months (b) experiencing moderate or worse average pain intensity in the past week, defined as ≥3 on 0–10 numeric rating scale (c) experiencing at least moderately severe pain catastrophizing, defined as ≥16 on the Pain Catastrophizing Scale; (d) access to a computer or mobile device with Internet access to participate in study treatment sessions; (e) at least 18 years of age; and (f) able to complete the study measures in English.

Exclusion criteria	(a) had severe cognitive impairment that prohibited participation in the intervention and/or assessments; (b) had active suicidal ideation; and/or (c) were experiencing active psychosis or other psychiatric or behavioural problems that would interfere with participating in the treatment.
Recruitment / selection of participants	Participants were recruited through the UW Medicine Multiple Sclerosis Center's embedded research recruitment mechanism, which offers research opportunities to consecutive patients who are interested in participating in research. In the case of this pilot, additional participants were identified through their prior participation in an observational study of individuals newly diagnosed with MS.
Intervention(s)	A psychological pain management intervention consisting of 120 min group videoconference and focused on developing an adaptive set of pain coping strategies based upon cognitive–behavioural theories of pain. The aim was to improve the participant's understanding of pain via education, as well as to reduce and/or buffer against maladaptive cognitions and pain behaviours. The intervention included didactic and skills building components with approximately 20 min devoted to each of the following: education on pain in MS and theoretical models of chronic pain and pain coping; relaxation training; a brief module on pacing; cognitive restructuring; and cognitive defusion. The sessions included 4 participants in each group who were also provided with an electronic supplement to follow along with during the sessions and facilitate recollection and skills practice after the completion of the treatment session. Additionally, participants received a list of online educational resources, self-help book recommendations, and guidance on how to identify a pain psychologist. The groups were delivered by a licensed rehabilitation psychologist with more than 10 years of experience in research and delivery of pain interventions. Participants were not prohibited from using other pain treatments, as this intervention was meant to be adjunctive to whatever existing treatments were being used.
Comparator	Usual Care Participants were instructed to continue with the care they would normally receive as part of their ongoing clinical care.
Number of participants	27 randomised
Duration of follow-up	1–2 weeks post completion of the study intervention ("post-treatment") 3 months (±2 weeks) following the treatment ("follow-up").
Indirectness	No indirectness
Additional comments	

1

Study arms

ENGAGE (N = 15)

Psychological pain management intervention delivered by video conference)

Usual Care (N = 12)

Characteristics

Arm-level characteristics

Characteristic	ENGAGE (N = 15)	Usual Care (N = 12)
% Female Sample size	n = 5 ; % = 33.3	n = 4 ; % = 33.3
Mean age (SD) (years) Mean (SD)	40.14 (11.2)	39.58 (12.3)
Relapsing remitting MS Sample size	n = 13 ; % = 86.7	n = 8 ; % = 66.7
Uncertain Sample size	n = 2 ; % = 13.3	n = 2 ; % = 16.7
Not available or CIS Sample size	n = 0 ; % = 0	n = 2 ; % = 16.7
Time since diagnosis (years) Mean (SD)	2.13 (1.15)	2.21 (0.9)

Outcomes

Study timepoints

- Baseline
- 3 month

ENGAGE compared to Usual Care at 3 months follow up

Outcome	ENGAGE , Baseline, N = 15	ENGAGE , 3-month, N = 15	Usual Care, Baseline, N = 12	Usual Care, 3-month, N = 12
Pain catastrophizing Mean (SD)	20.11 (7.77)	18.56 (10.88)	17.43 (10.22)	14.42 (9.97)
Pain intensity Mean (SD)	4.2 (1.62)	3.5 (1.9)	4.08 (1.56)	3.58 (1.68)
Pain interference (PROMIS) Mean (SD)	55.74 (4.81)	54.38 (9.23)	55.14 (7.65)	55.23 (6.83)
Depression (PHQ-8) Mean (SD)	10 (2.96)	8.44 (3.4)	5.55 (3.11)	6.41 (3.54)

Pain catastrophizing - Polarity - Lower values are better
Pain intensity - Polarity - Lower values are better
Pain interference (PROMIS) - Polarity - Lower values are better
Depression (PHQ-8) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Pain catastrophising_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Pain_intensity_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Pain interference (PROMIS)_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Depression (PHQ-8)_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Ayache, 2016

Bibliographic Reference	Ayache, S. S.; Palm, U.; Chalah, M. A.; Al-Ani, T.; Brignol, A.; Abdellaoui, M.; Dimitri, D.; Sorel, M.; Creange, A.; Lefaucheur, J. P.; Prefrontal tDCS Decreases Pain in Patients with Multiple Sclerosis; Frontiers in Neuroscience; 2016; vol. 10; 147

Study details

Secondary publication of another included	

study- see primary study for details	
Trial name / registration number	The trial is registered at the Deutsches Register Klinischer Studien (drksneu.uniklinik-freiburg.de) and has the following registration number: DRKS00005296.
Study location	France
Study setting	Hospital
Study dates	
Sources of funding	
Inclusion criteria	(i) a definite MS diagnosis according to the 2010 revised McDonald criteria (Polman et al., 2011); (ii) age between 18 and 70 years; (iii) right handedness based on the Edinburgh inventory (Oldfield, 1971); and (iv) a history of neuropathic pain since more than 3 months as per the Neuropathic Pain Symptom Inventory (NPSI; Bouhassira et al., 2004), with an intensity >40 on the visual analog scale from 0 to 100 (VAS0−100), obtained as the average of daily scores over a representative week.
Exclusion criteria	(i) MS relapses within the last 2 months; (ii) changes in pharmacological and physical therapies during the last month; (iii) the presence of comorbid neurodegenerative or psychiatric disorders; (iv) history of substance abuse; (v) absence of measurable pain related evoked potentials (PREPs) at the right hand; (vi) severe deficit in the visual acuity or fields as documented by an ophthalmic exam; and (vii) severe right upper limb impairment as per the Medical Research Council scale for muscle power (MRC) (Medical Research Council, 1981). For the latter, we applied the MRC score to the four muscle groups involved in pinching, wrist extension, forearm flexion, and arm abduction, so that the sum of their scores could vary between 0 (null strength) and 20 (full strength); an MRC score <12 excluded the individual from participation.
Recruitment / selection of participants	Patients were enrolled by the study investigators from the Neurology department of Henri Mondor Hospital, Créteil, France, between November 2012 and November 2014
Intervention(s)	A battery driven multi-channel direct current stimulator (Starstim, Neuroelectrics, Barcelona, Spain) delivered the direct current over the scalp through sponge electrodes (surface area = 25 cm2), soaked in a saline solution to minimize the

	risk of skin irritation (Palm et al., 2014). The stimulation electrodes were directly positioned on an adult sized cap worn by the patients, and labeled according to the 10–20 EEG system of electrode positioning (Starstim, Neuroelectrics, Barcelona, Spain). To stimulate the left DLPFC, the anode was placed over F3, and its corresponding cathode over the right supraorbital region (Figure 1). The used current intensity was 2 mA (total current density over the stimulated area: 0.06 mA/cm2) which is below the threshold for tissue damage (Poreisz et al., 2007; Nitsche et al., 2008). For the active stimulation, the current was ramped up during the first 15 s to a maximum of 2 mA that was maintained throughout the 20-min stimulation session. Sham or active anodal tDCS blocks were tested in a random order and were held apart by at least 3 weeks. Each block consisted of three consecutive daily tDCS sessions.
Population subgroups	
Comparator	Sham stimulation where the current was ramped down immediately after ramping up in order to achieve an effective blinding
Number of participants	16
Duration of follow-up	

Study arms

tDCS (N = 8)

Sham (N = 8)

Outcomes

Study timepoints

- Baseline

- 4 week

tDCS compared to sham for pain relief in MS

Outcome	tDCS , Baseline, N = 8	tDCS , 4-week, N = 8	Sham, Baseline, N = 8	Sham, 4-week, N = 8
VAS (0-100) Average measured 7 days before and 7 days after stimulation Mean (SD) Note: this pain outcome was favoured from the Ayache 2016 study as it could be pooled with another study. Other pain outcomes reported below study were extracted but not analysed.	51.2 (19.2)	43.1 (26.2)	52.1 (19.6)	50.3 (19.7)
BPI Global score Mean (SD)	9.2 (3.4)	9.9 (3.5)	8.2 (3.5)	9.9 (3.5)
BPI Severity subscale Mean (SD)	4.8 (2.4)	4.3 (2.1)	4.8 (2.4)	4.6 (2.1)
BPI Interference subscale Mean (SD)	4.5 (1.6)	3.9 (1.6)	5 (1.5)	4.6 (1.6)
Mean HADS total score Mean (SD)	14.1 (6.3)	13.6 (5.8)	14.4 (5.9)	14.5 (6.5)
Mean HADS Anxiety Mean (SD)	7.7 (3)	7.6 (3.6)	8.1 (3.4)	8.3 (3.9)

Outcome	tDCS , Baseline, N = 8	tDCS , 4-week, N = 8	Sham, Baseline, N = 8	Sham, 4-week, N = 8
Mean HADS Depression Mean (SD)	6.4 (3.9)	6 (3.3)	6.3 (3)	6.2 (3.3)

VAS (0-100) - Polarity - Lower values are better
Mean HADS Anxiety - Polarity - Lower values are better
Mean HADS Depression - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Cross-over trial
VAS (0-100)_4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

BPI Global score_4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

BPI Interference subscale_4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

HADS total score_4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

1
2 **HADS Anxiety_4 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

3
4 **HADS Depression_4 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

1

2 **Berra, 2019**

Bibliographic Reference	Berra, E.; Bergamaschi, R.; De Icco, R.; Dagna, C.; Perrotta, A.; Rovaris, M.; Grasso, M. G.; Anastasio, M. G.; Pinardi, G.; Martello, F.; Tamburin, S.; Sandrini, G.; Tassorelli, C.; The Effects of Transcutaneous Spinal Direct Current Stimulation on Neuropathic Pain in Multiple Sclerosis: Clinical and Neurophysiological Assessment; Frontiers in Human Neuroscience; 2019; vol. 13; 31

3

4 ## Study details

Trial name / registration number	NCT02331654
Study location	Italy
Sources of funding	supported by a grant of the Italian Multiple Sclerosis Foundation (FISM), 2012.
Inclusion criteria	Not reported
Exclusion criteria	(a) other neurological disorders, including primary or secondary headaches; (b) clinical or family history of neurological disorders; (c) any systemic or psychiatric disorder; (d) Beck Depression Inventory (BDI) scale score >9; (e) cognitive impairment (Mini Mental State Examination < = 24); (f) use of analgesics or steroids in the previous 24 h; (g) clinical or instrumental (including MRI) evidence of any central or peripheral disease/lesion potentially causing sensory impairment, including spinal lesions at lumbar level; (h) fibromyalgia; (i) complex regional pain syndrome; (j) chronic low

	back pain and other pain conditions not related to MS; and (k) changes in the schedule or dose of Disease Modifying Drugs (DMDs) for MS, antidepressants, antiepileptic drugs, tetrahydrocannabinol/cannabidiol or any other drug that may have a definite or potential effect on pain in the previous 3 months. Patients were excluded from the study if: - any change in the schedule or dose of drugs listed at point (l) above became necessary at any time during the observation period. - they had taken analgesics or steroids in the 24 h before the clinical and neurophysiological evaluations.
Recruitment / selection of participants	Patients were recruited at the IRCCS C. Mondino Foundation in Pavia, Santa Lucia Foundation in Rome, IRCCS ‘‘Neuromed’’ Institute in Pozzilli and Don Gnocchi Foundation in Milan, Italy
Intervention(s)	Anodal and sham ts-DCS was delivered by a constant direct current electrical stimulator (HDCstim, Newronika s.r.l., Milan, Italy) connected to a pair of electrodes: the anode was placed on the thoracic spinal cord (over the spinal process of the tenth thoracic vertebra) and the cathode (reference) on the right shoulder in the suprascapular region. Stimulating electrodes consisted in 1-mm thick, rectangular (7 × 5 cm), rubber membranes, enveloped in a saline-soaked sponge. Conducting surface was 35 cm2 for both active and reference electrode. Electrodes were fixed inside by elastic customized stripes. 2 mA constant direct current for 20 min in each session with a density of 0.071 mA/cm2 and delivered a total charge of 63.9 mC/cm2 . 10 daily 20-min sessions delivered over a 2-week period (from Monday to Friday) and a follow-up period of 4 week.
Comparator	Electrodes were placed in the same spots than real anodal stimulation, but the stimulator was programmed to automatically turn to 0 mA after 10 s. Ten daily 20-min sessions were delivered over a 2-week period (from Monday to Friday) and a follow-up period of 4 week.
Number of participants	33 participants; 19 randomised to anodal tcDCS and 14 to sham
Duration of follow-up	4 weeks
Indirectness	No indirectness
Additional comments	ITT

Study arms

Active ts-DCS (N = 19)

Sham (N = 19)

Characteristics

Arm-level characteristics

Characteristic	Active ts-DCS (N = 19)	Sham (N = 19)
% Female Sample size	n = 15 ; % = 78.9	n = 10 ; % = 71.4
Mean age (SD) (years) Mean (SD)	57.6 (9.1)	54 (7.79)
Relapsing-remitting Sample size	n = 1 ; % = 5.3	n = 3 ; % = 21.4
Secondary progressive Sample size	n = 14 ; % = 73.7	n = 10 ; % = 71.4
Primary progressive Sample size	n = 4 ; % = 21.1	n = 1 ; % = 7.1
Relapsing-remitting MS Mean (SD)	16 (5.7)	24.5 (7.1)
Secondary-progressive MS Mean (SD)	24.5 (7.1)	21 (9.3)
Primary-progressive MS	18.6 (10.5)	14 (0)

Characteristic	Active ts-DCS (N = 19)	Sham (N = 19)
Mean (SD)		
EDSS score Mean (SD)	5.9 (1.3)	5.9 (1.2)
Disease modifying drugs Sample size	n = 7 ; % = 36.8	n = 5 ; % = 35.7
cannabidiol Sample size	n = 3 ; % = 15.7	n = 3 ; % = 21.4
Other drugs for neuropathic pain Sample size	n = 8 ; % = 42.1	n = 7 ; % = 50

Outcomes

Study timepoints

- Baseline
- 4 week

ts-DCS compared to Sham for pain relief in MS

Outcome	Active ts-DCS, Baseline, N = 19	Active ts-DCS, 4-week, N = 19	Sham, Baseline, N = 14	Sham, 4-week, N = 14
NPSI Mean (SD)	37.4 (21.4)	21 (14.4)	10 (17.9)	33.7 (13.2)

NPSI - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
NPSI_4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Bogosian, 2015

Bibliographic Reference	Bogosian, A.; Chadwick, P.; Windgassen, S.; Norton, S.; McCrone, P.; Mosweu, I.; Silber, E.; Moss-Morris, R.; Distress improves after mindfulness training for progressive MS: A pilot randomised trial; Multiple Sclerosis; 2015; vol. 21 (no. 9); 1184-94

1 **Study details**

Trial name / registration number	Registered at the Current Controlled Trials database. Trial number ISRCTN93263909
Study location	Randomised controlled trial
Study setting	Home based via Skype
Study dates	Recruitment took place between December 2012 and May 2013. The treatment phase took place between February 2013 and July 2013.
Sources of funding	This work was supported by the MS Society UK (961/11).
Inclusion criteria	Inclusion criteria were diagnosis of PPMS or SPMS, Internet access and some level of distress determined by a score of 3 or greater on the General Health Questionnaire (GHQ-12).17 This cut off score was chosen following recommendations for MS
Exclusion criteria	Exclusion criteria were severe cognitive impairment, as determined by a score of 20 or smaller on the Telephone Interview for Cognitive Status-Modified (TICS-M)19 and high suicide risk, as assessed by a score of 20 or greater on the Clinical Outcome of Routine Evaluation (CORE-10). People were also excluded if they reported any serious psychological disorders (e.g., psychosis, substance abuse), severe hearing impairment, attending other psychological therapies or prior formal training in mindfulness.
Recruitment / selection of participants	Potential participants were recruited through adverts on the MS Society website and from National Health Service (NHS) MS centres across the UK. Recruitment took place between December 2012 and May 2013. Screening questionnaires were administered via telephone.
Intervention(s)	The mindfulness programme was delivered in 8 hour-long sessions over an 8-week period via Skype video conferences and restricted to 5 for each group. Participants could see each other and communicate as a group. The format and manual for the mindfulness group, including length of sessions and individual mindfulness practices, were developed in partnership with patients with MS through initial experimental case studies. The content of the manual was adapted from the Mindfulness-Based Cognitive Therapy (MBCT) course book. Participants discussed thoughts regarding having MS and how these thoughts are linked to anxiety and low mood. Each session, introduced key mindfulness concepts, addressed issues common to progressive MS, and described homework for the week ahead. Each session started with a 10-minute mindfulness practice, followed by discussion of this practice and the homework practice of the previous

	week. Then new concepts (e.g., acceptance, relating to thoughts and self-compassion) were introduced. The mindfulness teacher asked open questions to facilitate a deeper understanding of the concepts. Formal teaching/psycho-education was kept to a minimum. A five- to 10-minute mindfulness practice followed and finally homework for the next week was set. A daily home practice of 10–20 minutes was set, and audio compact discs (CDs) produced specifically for this course were provided. Guidance in the CD practices reflected challenges of MS, such as lack of sensations or difficulties retaining a posture. Participants were encouraged to keep a diary of home practice, but, in fact, very few did record it. A health psychologist facilitated the courses supervised a clinical psychologist and expert mindfulness practitioner.
Population subgroups	
Comparator	Participants allocated to the waiting-list group received the treatment they would normally expect within the NHS. People may receive a mix of clinical input and review from both primary and secondary care providers, according to individual health needs.
Number of participants	40 (19 mindfulness; 21 waiting-list)
Duration of follow-up	3 months Results also reported for baseline (prior to randomisation) and post-intervention (unclear time point)
Indirectness	No indirectness
Additional comments	Intention-to-treat

Study arms

Mindfulness (N = 19)

Delivered through Skype videoconference

Waiting list (N = 21)

Characteristics

Arm-level characteristics

Characteristic	Mindfulness (N = 19)	Waiting list (N = 21)
% Female Sample size	n = 9 ; % = 47.5	n = 13 ; % = 61.9
Mean age (SD) Mean (SD)	53.42 (8.3)	50.9 (9.9)
Ethnicity White British Sample size	n = 17 ; % = 89.5	n = 19 ; % = 90.5
Years since diagnosis Mean (SD)	16.24 (12.57)	12.57 (8.6)
Primary progressive MS (No other types reported) Sample size	n = 5 ; % = 26.3	n = 12 ; % = 57.1
EDSS Mean (SD)	6.8 (1.6)	6.2 (1.4)

Outcomes

Study timepoints

- 3 month

Mindfulness compared to waiting list for MS patients

Outcome	Mindfulness , 3-month, N = 19	Waiting list, 3-month, N = 21
Distress (GHQ) Mean (SD)	9.93 (5.02)	15.17 (4.42)
Depression (HADS) Mean (SD)	5.13 (4.27)	7.28 (3.27)
Anxiety (HADS) Mean (SD)	4.84 (3.21)	7.37 (3.96)
MSIS psychological Mean (SD)	18.72 (6.31)	23.76 (7.42)
MSIS physical Mean (SD)	60.64 (20.52)	19.2 (*empty data*)
Pain (NRS) Mean (SD)	1.73 (2.09)	4.28 (2.85)
EQ-5D Mean (SD)	0.51 (0.37)	0.5 (0.29)

Distress (GHQ) - Polarity - Lower values are better
Depression (HADS) - Polarity - Lower values are better
Anxiety (HADS) - Polarity - Lower values are better
MSIS psychological - Polarity - Lower values are better
MSIS physical - Polarity - Lower values are better
Pain (NRS) - Polarity - Lower values are better

EQ-5D - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT Distress (GHQ)_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Depression_HADS_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Anxiety_HADS_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

MSIS psychological_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

MSIS physical_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Pain (NRS)_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

EQ-5D_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Doulatabad, 2012

Bibliographic Reference	Doulatabad, S. N.; Nooreyan, K.; Doulatabad, A. N.; Noubandegani, Z. M.; The effects of pranayama, hatha and raja yoga on physical pain and the quality of life of women with multiple sclerosis; African journal of traditional, complementary, & alternative medicines; 2012; vol. 10 (no. 1); 49-52

Study details

Secondary publication of another included	

study- see primary study for details	
Trial name / registration number	
Study location	Iran
Study setting	
Study dates	The study was carried out from July 2009 to May 2010
Sources of funding	Yasouj University of Medical Sciences
Inclusion criteria	1) women between 18- 45, 2) with at least 2 year- MS history, and 3) the agility to exercise Yoga.
Exclusion criteria	Women suffering from epilepsy, cardiovascular, metabolic and psychiatric diseases, those in the acute phase of the disease, and those simultaneously included into other sorts of self-care programmes aiming to improve their quality of life.
Recruitment / selection of participants	Patients' names were requested from the University deputy for treatment and those who met the inclusion criteria were accepted and enrolled into the study. Participants were contacted by phone or visited at home. An invitation from the regional Yoga Association was sent to the case group and after explaining the purpose of the contact, the women were invited to attend Yoga classes.
Intervention(s)	Participants in the intervention group underwent Yoga therapy for three months, keeping the pace of eight 60 to 90 minute-lasting sessions per month, while the control group was subjected to no intervention at all.

	The Yoga method exercised in the case group is based on the Ashtanga Yoga having an eight-folded path founded on three principles: 1) slow-motion exercising (Hatha), 2) breathing exercises or life force absorption through Yoga breathing (Pranayama), and 3) mind focus and the establishment of control through meditation, extension and quiescence (Raja).
Comparator	No intervention
Number of participants	60 (randomised 30 Yoga; 30 no intervention)
Duration of follow-up	1 month
Indirectness	No indirectness
Additional comments	Not reported

Study arms

Yoga (N = 30)

No intervention (N = 30)

Characteristics

Study-level characteristics

Characteristic	Study (N = 60)
% Female Sample size	n = 60 ; % = 100
Mean age (SD) Mean (SD)	31.6 (8)

Outcomes

Study timepoints

- Baseline
- 1 month

Yoga compared to no intervention for managing pain in MS patients

Outcome	Yoga , Baseline, N = 30	Yoga , 1 month, N = 30	No intervention , Baseline, N = 30	No intervention , 1 month, N = 30
Pain (MSQoL-54) Mean (SD)	4.8 (5.12)	3.8 (4.16)	3.4 (4.1)	3.3 (4.2)
Quality of Life (MSQoL-54) Mean (SD)	4.9 (1.9)	7.4 (2.16)	6.9 (1.5)	6.8 (1.9)

Pain (MSQoL-54) - Polarity - Higher values are better
Quality of Life (MSQoL-54) - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Pain (MSQoL-54)_1 month

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Quality of life (MSQoL-54)_1 month

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Dunne, 2021

Bibliographic Reference	Dunne, J.; Chih, H. J.; Begley, A.; Daly, A.; Gerlach, R.; Schutze, R.; Castell, E.; Byrne, J.; Black, L. J.; A randomised controlled trial to test the feasibility of online mindfulness programs for people with multiple sclerosis; Multiple Sclerosis and Related Disorders; 2021; vol. 48; 102728

Study details

Trial name / registration number	ACTRN12618001922268
Study type	Randomised controlled trial (RCT)
Study location	Australia
Study setting	Online
Study dates	Not reported
Sources of funding	Not stated
Inclusion criteria	Adults ≥18 years with any type of MS. Not highly distressed as assessed by the Kessler Psychological Distress Scale (score ≥30), Not cognitively impaired Standardised Mini-Mental State Examination score ≥24, able to speak and understand English and have access to internet.
Exclusion criteria	Not stated
Recruitment / selection of participants	Participants were recruited across Australia using newsletters and social media through the networks of MS Research Australia, MS Western Australia and other Australian service providers.
Intervention(s)	**Mindfulness for MS (M4MS)**

	A programme was adapted from mindfulness based cognitive therapy which introduced participants to mindfulness meditation and mindful movement and psychoeducation. It focussed on helping participants to work skilfully with pain, discomfort and emotions that automatically occur when facing difficulties with the experiences of MS. A trained psychologist delivered the programme in 8 weekly two-hour sessions via Zoom. **Chair Yoga** Delivered online via Zoom by a registered Yoga teacher and focussed on simple movements incorporating breathing and relaxation techniques that were adapted from traditional Hatha Yoga with movements conducted while seated in chair
Comparator	Control Wait list
Number of participants	55 randomised; 18 M4MS, 18 chair Yoga and 19 waitlist
Duration of follow-up	8 weeks
Indirectness	No indirectness
Additional comments	ITT

Study arms

Mindfulness for Multiple Sclerosis (M4MS) (N = 18)

An adapted mindfulness based cognitive therapy including mindfulness meditation, mindful movement and psycho-education.

Chair Yoga (N = 18)

Breathing and relaxation techniques adapted from traditional Hatha Yoga with movements conducted while seated in a chair.

Wait-list control (N = 19)

Characteristics

Arm-level characteristics

Characteristic	Mindfulness for Multiple Sclerosis (M4MS) (N = 18)	Chair Yoga (N = 18)	Wait-list control (N = 19)
% Female Sample size	n = 14 ; % = 82.4	n = 14 ; % = 77.5	n = 17 ; % = 89
Mean age (SD) Mean (SD)	44.6 (10.1)	48.2 (10.4)	51.2 (11.9)
Years since diagnosis Median (IQR)	8 (10)	7.5 (12)	10 (11)

Outcomes

Study timepoints

- 1 week

Mindfulness or exercise for pain relief in MS

Outcome	Mindfulness for Multiple Sclerosis (M4MS), 1 week, N = 16	Chair Yoga , 1 week, N = 18	Wait-list control , 1 week, N = 16
MSQOL 54 Bodily pain scale Median (IQR)	50 (100)	0.0 (50)	0.0 (50)

Outcome	Mindfulness for Multiple Sclerosis (M4MS), 1 week, N = 16	Chair Yoga , 1 week, N = 18	Wait-list control , 1 week, N = 16
MSQoL-54 Health distress scale Median (IQR)	62.5 (32.5)	52.5 (50)	60 (40)
MSQoL-54 Overall quality of life Median (IQR)	79.2 (18.3)	70.9 (21.7)	63.4 (31.7)
BPI Interference subscale Median (IQR)	12 (35.5)	22.5 (36)	16 (40)
BPI Severity subscale Median (IRQ)	4.5 (17)	10 (10)	12 (20)
BPI Global score Median (IQR)	42.5 (60)	60 (60)	57.5 (70)

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
MSQOL 54 Bodily pain scale_1 week_mindfulness vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

MSQOL 54 Bodily pain scale_1 week_yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

MSQOL 54 Bodily pain scale_1 week_mindfulness vs. yoga

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

MSQoL-54 Health distress scale_1 week_mindfulness vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

MSQoL-54 Health distress scale_1 week_yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

MSQoL-54 Health distress scale_1 week_mindfulness vs. yoga

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

MSQoL-54 Overall quality of life_1 week_mindfulness vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

MSQoL-54 Overall quality of life_1 week_yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

MSQoL-54 Overall quality of life_1 week_mindfulness vs. yoga

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

BPI Interference subscale_1 week_mindfulness vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

BPI Interference subscale_1 week_yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

BPI Interference subscale_1 week_mindfulness vs. yoga

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

BPI Severity subscale_1 week_mindfulness vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

BPI Severity subscale_1 week_yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

BPI Severity subscale_1 week_mindfulness vs. yoga

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

BPI Global score_1 week_mindfulness vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

BPI Global score_1 week_yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

BPI Global score_1 week_mindfulness vs. yoga

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Ehde, 2015

Bibliographic Reference	Ehde, D. M.; Elzea, J. L.; Verrall, A. M.; Gibbons, L. E.; Smith, A. E.; Amtmann, D.; Efficacy of a Telephone-Delivered Self-Management Intervention for Persons With Multiple Sclerosis: A Randomized Controlled Trial With a One-Year Follow-Up; Archives of Physical Medicine & Rehabilitation; 2015; vol. 96 (no. 11); 1945-58.e2

1 **Study details**

Trial name / registration number	NCT00944190
Study location	USA
Study setting	Outpatient
Study dates	Study conducted between April 2011 and September 2013
Sources of funding	StataCorp LP mentioned as a 'supplier'.
Inclusion criteria	aged ≥18 years; self-reported physician diagnosis of MS; and at least one of the following: moderate depressive symptoms (score 10-14 on PHQ-9), presence of chronic pain (average pain intensity ≥3 in past week on 0-10 numeric rating scale) or significant fatigue symptoms (score ≥10 on 5-item Modified Fatigue Impact Scale Short Form).
Exclusion criteria	significant cognitive impairment (≥1 error on 6-item Cognitive Screener); currently in psychotherapy more than once each month; participated in another study for fatigue, depression or pain; and exhibited moderate-severe or severe depressive symptoms (PHQ-9 score ≥15).
Recruitment / selection of participants	Recruited from mailings to individuals in University of Washington Department of Rehabilitation Medicine Research Registry, advertisements through national MS organistions, flyers/referrals from University of Washington MS Center, ClinicalTrials.gov and other active studies in the department.
Intervention(s)	Telephone-delivered self-management intervention. Evidence-based cognitive behavioural and positive psychological strategies to aid participants in the self-management of pain, depression and fatigue in daily life. At final session, therapist and participant created comprehensive personal self-management plan integrating their preferred skills and goals to use post-treatment. Both interventions used therapist manuals and participant workbooks informed by qualitative research. Piloted and revised based on feedback from 8 participants. Consisted of 8 weekly 45-60 min telephone sessions with 15-min follow-up calls at 4- and 8-weeks post-treatment. Interventions delivered by therapists that had received training and supervision from the principal investigator (psychologist with >20 years expertise in study population and interventions).
Population subgroups	None reported

Comparator	Control - telephone-delivered education intervention. Aimed to inform participants about fatigue, pain and depression and other common MS challenges without teaching, rehearsing or prescribing any specific self-management skills. Interactive discussion encouraged. Designed to be a credible comparator that controlled for natural history, measurement processes and common factors such as therapist attention, therapeutic relationship, treatment dosing and participation in a manualised intervention. Both interventions used therapist manuals and participant workbooks informed by qualitative research. Piloted and revised based on feedback from 8 participants. Consisted of 8 weekly 45-60 min telephone sessions with 15-min follow-up calls at 4- and 8-weeks post-treatment. Interventions delivered by therapists that had received training and supervision from the principal investigator (psychologist with >20 years expertise in study population and interventions).
Number of participants	163 randomised and included in intention to treat analysis
Duration of follow-up	Follow-up up to 12 months after starting intervention (10 months after the last session), with results reported at 6- and 12-month time-points relevant to the protocol
Indirectness	Serious - includes proportion where fatigue was not one of the reasons for inclusion in the study (81.6% met criteria for fatigue).
Additional comments	Patients could continue existing medical treatments for pain, depression of fatigue. Intention to treat used for some analyses but per protocol where missing data was too high to run model as intention to treat.

Study arms

Self-management intervention (N = 75)

Telephone delivered

MS education (N = 88)

Telephone delivered

Characteristics

Arm-level characteristics

Characteristic	Self-management intervention (N = 75)	MS education (N = 88)
% Female Sample size	n = 67 ; % = 89.3	n = 75 ; % = 85.2
Mean age (SD) Mean (SD)	51 (10.1)	53.2 (10)
Non-hispanic white Sample size	n = 62 ; % = 82.7	n = 74 ; % = 84.1
Non-hispanic black Sample size	n = 9 ; % = 12	n = 10 ; % = 11
Hispanic > 1 race Sample size	n = 2 ; % = 2.7	n = 1 ; % = 1.1
Non-Hispanic and >1 race Sample size	n = 2 ; % = 2.7	n = 3 ; % = 3.4
Comorbidities Text	NR	NR

Outcomes

Study timepoints

- Baseline
- 12 month

- 6 month

Self-management compared to education for pain in MS

Outcome	Self-management intervention , Baseline, N = 75	Self-management intervention , 12-month, N = 75	Self-management intervention , 6-month, N = 75	MS education , Baseline, N = 88	MS education , 12-month, N = 88	MS education , 6-month, N = 88
>30% reduction in pain Sample size	n = 23 ; % = 47	n = 20 ; % = 43	n = NR ; % = NR	n = 22 ; % = 36	n = 28 ; % = 47	n = NR ; % = NR
Pain interference (BPI) Mean (SD)	3.7 (2.4)	3 (2.3)	2.8 (2.3)	3.7 (2.4)	2.8 (2.3)	3 (2.6)
Depression (PHQ-9) Mean (SD)	8.6 (4)	6.3 (4.2)	5.7 (4.7)	10.2 (4.3)	7.3 (5)	6.7 (4.2)
Pain Intensity (NRS) Mean (SD)	3.7 (2.2)	3.4 (2)	3.3 (2.1)	3.7 (1.8)	2.9 (2.1)	3.1 (2.3)
Physical HRQoL (SF-8) Mean (SD)	37.3 (8.7)	38.6 (8.6)	40.3 (9.5)	38.9 (7.4)	40.3 (9.1)	40.4 (9.2)

Outcome	Self-management intervention , Baseline, N = 75	Self-management intervention , 12-month, N = 75	Self-management intervention , 6-month, N = 75	MS education , Baseline, N = 88	MS education , 12-month, N = 88	MS education , 6-month, N = 88
Mental HRQoL (SF-8) Mean (SD)	44.2 (9.3)	47.7 (9.2)	48.2 (9.8)	43.4 (9.2)	47.2 (10)	47 (9.5)

Pain interference (BPI) - Polarity - Lower values are better
Depression (PHQ-9) - Polarity - Lower values are better
Pain Intensity (NRS) - Polarity - Lower values are better
Physical HRQoL (SF-8) - Polarity - Higher values are better
Mental HRQoL (SF-8) - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Pain interference (BPI)_12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Depression (PHQ-9)_12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(> 12 months follow up)*

1 **Physical HRQoL (SF-8)_12months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(> 12 months follow up)*

2

3 **Mental HRQoL (SF-8)_12 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(> 12 months follow up)*

Pain interference (BPI)_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Gromisch, 2020

Bibliographic Reference	Gromisch, E. S.; Kerns, R. D.; Czlapinski, R.; Beenken, B.; Otis, J.; Lo, A. C.; Beauvais, J.; Cognitive Behavioral Therapy for the Management of Multiple Sclerosis-Related Pain: A Randomized Clinical Trial; International Journal of Ms Care; 2020; vol. 22 (no. 1); 8-14

Study details

Trial name / registration number	
Study location	USA
Sources of funding	Support for this project was provided by the US Department of Veterans Affairs, Rehabilitation Research and Development Service (D4150R) and Health Services Research and Development Service, Center of Innovation (COIN), Pain Research, Informatics, Multimorbidities, and Education (PRIME) Center, West Haven, CT (CIN 13-047).
Inclusion criteria	The criteria for inclusion were a confirmed diagnosis of MS with at least 3 months of MS-related pain (e.g., neuropathic pain, pain related to muscle spasms, neuralgias) of at least moderate intensity, defined as a score of 4 or greater on the 0 (no pain) to 10 (worst pain imaginable) Numeric Rating Scale (NRS).1
Exclusion criteria	Persons with life-threatening or acute physical illnesses (e.g., cancer, end-stage renal disease), current alcohol or substance abuse or dependence (defined as active use within the past 3 months), current psychosis, suicidal or homicidal ideation as noted in medical progress notes or inpatient psychiatric hospitalization within the past 3 months, or pending surgical or interventional pain management procedures were excluded. Persons with MS with physical disabilities (e.g., severe dysarthria) or profound cognitive impairments that would have impeded successful participation in the treatment sessions were also excluded. If persons had two or more documented exacerbations (i.e., an event attributed to new disease activity by their treating neurologists and causing a clinically significant worsening of existing symptoms or development of new symptoms) during the past year or experienced an exacerbation within 24 hours of enrolment, they were excluded until they completed 1 month of appropriate treatment or were 3 months post exacerbation.

Recruitment / selection of participants	Participants were recruited from the greater Yale–New Haven community (New Haven, CT), VA Connecticut Healthcare System (VACHS) (West Haven, CT), VA Boston Healthcare System (VABHS) (Boston, MA), and Griffin Hospital (Derby, CT), as well as through the National MS Society and the Connecticut MS Society. Potential participants identified via the VACHS and Yale MS Center were sent opt-in letters describing the study and eligibility criteria and inviting their participation.
Intervention(s)	12 sessions, including seven 60-minute, outpatient, individual sessions and five 30-minute individual telephone sessions. Both treatment arms were delivered by clinical health psychologists with training in care of persons with MS and delivering CBT for chronic pain. The protocol also incorporated motivational interviewing strategies to encourage treatment engagement and adherence to therapist recommendations for pain coping skill practice. Treatment was tailored and paced according to participant interests, previous knowledge, and learning capacity. Components of CBT treatment included 1) identification of idiosyncratic beliefs about pain and pain treatment, 2) instruction in cognitive (e.g., distraction) and behavioural (eg, activity pacing) skills, and 3) consolidation of cognitive and behavioural skills through activities such as role-playing. As a method to reinforce material presented during the session, each participant collaborated with the psychologist to develop intersession behavioural goals and plans for using pain coping skill practice in the form of “homework.” This allowed psychologists to provide corrective feedback. + Standard care Participants continued to receive routine care for their MS and MS-related symptoms, including pain management, from their current health care providers (not research staff). Standard of care usually consisted of being seen in an outpatient specialty clinic by a neurologist who collaborated with other clinicians to care for patients in all stages of the disease. No efforts were made to influence the management of MS, MS-related pain, or other health concerns. Medication use, including changes in medication, self-reported adherence, and extra doses of pain medications, however, were monitored by participant completion of a weekly questionnaire.
Comparator	12 sessions, including seven 60-minute, outpatient, individual sessions and five 30-minute individual telephone sessions. Both treatment arms were delivered by clinical health psychologists with training in care of persons with MS and delivering CBT for chronic pain. Topics for the 12 sessions include information on MS etiology, diagnosis and prognosis, pain in MS, medications for symptom management, disease-modifying medications, alternative therapies, rehabilitation, exercise, lifestyle issues, alcohol use and smoking, preventive health, adapting the home and assistive

	devices, and caregiver support. Topics that were psychological in nature, such as the emotional aspects of MS, were not included in the sourcebook. + Standard care Participants continued to receive routine care for their MS and MS-related symptoms, including pain management, from their current health care providers (not research staff). Standard of care usually consisted of being seen in an outpatient specialty clinic by a neurologist who collaborated with other clinicians to care for patients in all stages of the disease. No efforts were made to influence the management of MS, MS-related pain, or other health concerns. Medication use, including changes in medication, self-reported adherence, and extra doses of pain medications, however, were monitored by participant completion of a weekly questionnaire.
Number of participants	20 randomised; 10 CBT/SC and 10 ED/SC
Duration of follow-up	15 weeks
Indirectness	No indirectness
Additional comments	

Study arms

CBT/SC (N = 10)

Cognitive behavioural therapy in addition to standard care

ED/SC (N = 10)
MS-related education in addition to standard care

Characteristics

Arm-level characteristics

Characteristic	CBT/SC (N = 10)	ED/SC (N = 10)
% Female Sample size	n = 4 ; % = 40	n = 4 ; % = 40
Mean age (SD) Mean (SD)	52.2 (9.61)	53 (12.66)
Relapsing-remitting Sample size	n = 8 ; % = 80	n = 6 ; % = 60
Relapsing progressing Sample size	n = 1 ; % = 10	n = 1 ; % = 10
Primary-progressive Sample size	n = 1 ; % = 10	n = 1 ; % = 10
MS duration (years) Mean (SD)	12.6 (7.4)	13.9 (12.86)
Pain duration (years) Mean (SD)	11.3 (10.24)	15.15 (15.61)

Outcomes

Study timepoints

- Baseline
- 15 week

CBT compared to education for pain relief in MS

Outcome	CBT/SC, Baseline, N = 10	CBT/SC, 15-week, N = 10	ED/SC, Baseline, N = 10	ED/SC, 15-week, N = 10
Pain Severity A composite score using the NRS, the WHYMPI Pain Severity subscale, and the McGill Evaluative subscale Mean (SD)	4.11 (1.38)	3.78 (0.94)	4.28 (1.08)	3.57 (1.4)
Pain interference (WHYMPI Interference subscale). Mean (SD)	2.9 (1.31)	2.36 (1.33)	4.64 (0.93)	3.96 (1.42)
Beck Depression Inventory Mean (SD)	10.37 (5.72)	8.36 (5.56)	16.32 (7.23)	10.85 (8.12)

Pain Severity - Polarity - Lower values are better
Beck Depression Inventory - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Pain severity_15 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Pain interference (WHYMPI interference subscale)_15 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Beck Depression Inventory_15 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Grubic Kezele, 2020

Bibliographic Reference	Grubic Kezele, T.; Babic, M.; Kauzlaric-Zivkovic, T.; Gulic, T.; Combined upper limb and breathing exercise programme for pain management in ambulatory and non-ambulatory multiple sclerosis individuals: part II analyses from feasibility study; Neurological Sciences; 2020; vol. 41 (no. 1); 65-74

1 Study details

Trial name / registration number	NTC03222596.
Study location	Croatia
Study setting	MS Society Center - outpatient
Sources of funding	This work has been supported in part by the University of Rijeka
Inclusion criteria	Diagnosis of MS with mild to severe disability (EDSS score between 0.0 [normal neurological exam] and 8.0 [essentially restricted to wheelchair, retains many self-care functions, generally has effective use of arms]), adults between the age of 18 and 70 years, patients with Standardized Mini-Mental State Examination [19] > 24 and with no contraindications for performing breathing and UL exercises.
Exclusion criteria	An exacerbation of MS or corticosteroid treatment within the past 4 weeks, the presence of concomitant neurological and musculoskeletal disorders affecting arms, acute or chronic lung pathologies, breathing difficulties or any other serious illness that might interfere with the intervention
Recruitment / selection of participants	The patients with diagnosed MS were randomly selected based on the previous EDDS score from the MS Society Center (MSCC) register and their interest in participating was established by phone.
Intervention(s)	The exercise group exercised under physiotherapist guidance performing strengthening, coordination stretches and breathing exercises. They exercised 2 days/week, 60 min/session in the MSSC and performed independent home exercise 3 days/week for 4 weeks, at least 20 min/session. Adherence was monitored every week by registering the number of completed sessions at the MSSC and at home. The amount of physical activity performed with HE was monitored 2/week by asking the number of sessions per week and duration of each exercise during a session. The on-going physical therapy (without UL and breathing exercises 2/week for 45 min) was unchanged during the study for all patients (exercise and control group). At the end of the study (day after the last session), outcome measures were collected by the same independent researcher who assessed the baseline data.
Population subgroups	According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - mixed

	· According to disability (EDSS <6 and EDSS ≥6) - over 6 · Disease modifying treatment status (currently using and not currently using) - mixed · Group vs individual - group and home based · Delivered remotely vs in person - in person Reports data separately for ambulatory and non-ambulatory groups, threshold used to define this unclear but median EDSS in two groups was <6.0 (3.0-4.75 in the two groups) and ≥6.0 (7.0 in both groups), respectively.
Comparator	The control group performed no exercise during the investigation, but they were required to visit the MSSC 2 days/week (≤ 60 min) where they could freely socialize, having thereby approximately the same contact with the investigators as the exercise group. The control group was offered the exercise program at the end of the study, which everyone accepted. The on-going physical therapy (without UL and breathing exercises 2/week for 45 min) was unchanged during the study for all patients (exercise and control group). At the end of the study (day after the last session), outcome measures were collected by the same independent researcher who assessed the baseline data.
Number of participants	19 randomised and analysed
Duration of follow-up	4 weeks - end of treatment
Indirectness	Results reported separately for ambulatory and non-ambulatory groups but combined for the purpose of this review.

Study arms

Exercise (N = 10)

Combined upper limb and breathing exercise for home-based program

Control (N = 9)

Characteristics

Arm-level characteristics

Characteristic	Exercise (N = 10)	Control (N = 9)
% Female Sample size	n = 4 ; % = 40	n = 3 ; % = 33
Mean age (SD) Mean (SD)	53.9 (10.7)	48.2 (9.3)
Relapsing-remitting MS Sample size	n = 4 ; % = 40	n = 6 ; % = 67
Primary-progressive MS Sample size	n = 2 ; % = 20	n = 0 ; % = 0
Secondary-progressive MS Sample size	n = 4 ; % = 40	n = 3 ; % = 33
EDSS Expanded Disability Status Scale. Scale 0-10. Higher indicates higher disability. Median (range)	6.5 (1.0-8.0)	7.0 (1.0-7.5)
Interferon beta-1a Sample size	n = 1 ; % = 10	n = 0 ; % = 0
Fingolimod Sample size	n = 1 ; % = 10	n = 1 ; % = 11

Characteristic	Exercise (N = 10)	Control (N = 9)
Azathioprine Sample size	n = 0 ; % = 0	n = 1 ; % = 11
Glatiramer acetate Sample size	n = 1 ; % = 10	n = 2 ; % = 22
None Sample size	n = 7 ; % = 70	n = 5 ; % = 56

Outcomes

Study timepoints

- Baseline
- 4 week

Combined upper limb and breathing exercise for pain relief in MS

Outcome	Exercise , Baseline, N = 10	Exercise , 4-week, N = 10	Control, Baseline, N = 9	Control, 4-week, N = 9
Pain (VAS 0-5) Mean (SD)	2.6 (2.36)	1.4 (1.97)	3.13 (2.78)	3.4 (2.62)
Barthel Index (0-100) Mean (SD)	74 (18.89)	77.9 (17.92)	75.44 (18.28)	75.91 (18.69)
SF 36 General Health (0-100) Mean (SD)	48 (16.9)	49.5 (11.8)	46.7 (21.6)	41.1 (24.1)

Outcome	Exercise , Baseline, N = 10	Exercise , 4-week, N = 10	Control, Baseline, N = 9	Control, 4-week, N = 9
SF-36 Pain Mean (SD)	66.8 (29.3)	76.3 (28.2)	65 (42.7)	64.2 (36.4)
SF-36 physical functioning Scale 0-100 Mean (SD)	32.5 (31.9)	38.5 (34.8)	45.6 (43.4)	43.9 (43.9)
SF-36 Physical Limitations Mean (SD)	30 (24.4)	50 (30.6)	41.2 (45.7)	44.4 (43)
SF-36 Emotional Wellbeing Mean (SD)	71.4 (25.9)	75.6 (18.9)	66.4 (15.8)	64 (15.8)
SF-36 Emotional Limitation Mean (SD)	80.1 (37.8)	86.7 (33.9)	51.8 (44.1)	59.1 (42.7)

Barthel Index (0-100) - Polarity - Higher values are better
SF 36 General Health (0-100) - Polarity - Higher values are better
SF-36 Pain - Polarity - Higher values are better
SF-36 physical functioning - Polarity - Higher values are better
SF-36 Physical Limitations - Polarity - Higher values are better
SF-36 Emotional Wellbeing - Polarity - Higher values are better
SF-36 Emotional Limitation - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Pain (VAS 0-5)_4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Barthel Index (0-100)_4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

SF36 General Health (0-100)_4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **SF-36 Pain_4 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **SF-36 physical functioning_4 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

SF-36 Physical Limitations_4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **SF-36 Emotional Wellbeing_4 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **SF-36 Emotional Limitation_4 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1

2 **Hasanpour Dehkordi, 2016**

Bibliographic Reference	Hasanpour Dehkordi, A.; Influence of yoga and aerobics exercise on fatigue, pain and psychosocial status in patients with multiple sclerosis: a randomized trial; Journal of Sports Medicine & Physical Fitness; 2016; vol. 56 (no. 11); 1417-1422

3

4 **Study details**

Trial name / registration number	RCT2013063013768N2
Study location	Iran
Study setting	Yoga and aerobics exercises were implemented in the Sports Hall of Shahrekord University of Medical Sciences in addition to practice at home
Study dates	Not reported
Sources of funding	Supported by the Research and Technology Deputy of Shaherekord University of Medical Sciences
Inclusion criteria	Definite diagnosis of MS, consent to participate and ability to speak and to move to perform daily activities.
Exclusion criteria	Lack of ability to complete exercises or cooperate for any reason

Intervention(s)	Yoga: three sessions (60-70 min) weekly for 12 weeks. Hatha yoga (breathing techniques, postures and meditation). Stretching followed by standing, supine, prone-lying and sitting postures. Each pose held for 10-30 seconds with rest periods in between of 30 seconds to 1 min. Emphasis on breathing for relaxation and concentration during the classes. Each session ended with a 10 min deep relaxation session. Practice at home was recommended. Given leaflet detailing the poses to allow practice at home. Performed in a sports centre or gym near the hospital and supervised by a nurse and neurologist. All poses planned based on individual need. Aerobic exercise: three sessions (40 min) weekly for 12 weeks. Consisted of 5-10 min warm-up, 25-30 min exercise (walking) and 5 min cooling down. Performed at sports centre or gym near to the hospital. Supervised by nurse or a neurologist. Target was to reach 60% of heart rate reserve when exercising. After 6 sessions, duration of walking increased to 30-35 min and heart rate to 70% heart rate reserve. Each individual exercised based on their ability and resistance. Stopped when participants were physically tired or experienced severe dyspnoea, fatigue, dizziness or other problems that could be a risk to health based on Rhoten Fatigue Scale.
Comparator	Control: no exercise protocol. Educational support. Asked to maintain prescribed medications and usual lifestyle and were supervised by their nurse and physicians.
Number of participants	N=90 randomised, n=61 analysed During the study, 10 from case group and 10 from control group were excluded because of failure to cooperate, exacerbation of the disease, and family problems.
Duration of follow-up	12 weeks - end of treatment
Indirectness	None

Study arms

Yoga (N = 30)

Hatha yoga (60-70 minutes) three times a week for 12 weeks

Aerobic exercise (N = 30)
Aerobic exercise with walking as the main component. Three sessions a week for 12 weeks.

Control (N = 30)
Educational support without exercise

Characteristics

Study-level characteristics

Characteristic	Study (N = 61)
% Female Sample size	n = 60 ; % = 98
Mean age (SD) Mean	31.9
Ethnicity Custom value	Not reported
Comorbidities Custom value	Not reported

Outcomes

Study timepoints

- Baseline
- 12 week

Yoga or aerobic exercise for pain relief in MS

Outcome	Yoga , Baseline, N = 20	Yoga , 12-week, N = 20	Aerobic exercise, Baseline, N = 20	Aerobic exercise, 12-week, N = 20	Control, Baseline, N = 21	Control, 12-week, N = 21
SF-36 Mental Health Mean (SD)	53.9 (13.67)	60.54 (14.44)	54.87 (8.54)	61.78 (10.87)	52.4 (16.56)	50.44 (14.45)
SF-36 Body Pain Mean (SD)	43.24 (6.98)	38.54 (9.25)	44.54 (8.4)	39.65 (11.9)	45.12 (10.54)	55.71 (9.47)
SF-36 Limited activity following emotional problems Mean (SD)	41.9 (9.16)	35.65 (12.3)	39.4 (12.8)	36.23 (12.65)	42.11 (4.7)	47.15 (11.65)
SF-36 Limited activity following physical problems Mean (SD)	49.14 (11.41)	45.45 (11.41)	52.1 (14.44)	46.14 (13.45)	48.12 (13.87)	52.14 (12.4)
SF-36 General Health Mean (SD)	46.24 (11.69)	51.22 (8.65)	47.65 (9.52)	55.23 (10.96)	48.54 (7.45)	42.65 (9.25)

SF-36 Mental Health - Polarity - Higher values are better
SF-36 Body Pain - Polarity - Higher values are better
SF-36 Limited activity following emotional problems - Polarity - Higher values are better
SF-36 Limited activity following physical problems - Polarity - Higher values are better
SF-36 General Health - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

SF-36 Mental Health_12 weeks_yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

SF-36 Body Pain_12 weeks_yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

SF-36 Limited activity following emotional problems_12 weeks_yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

SF-36 Limited activity following physical problems_12 weeks_yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

SF-36 General Health_12 weeks_yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

SF-36 Mental Health_12 weeks_aerobic exercise vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **SF-36 Mental Health_12 weeks_aerobic exercise vs. yoga**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **SF-36 Body Pain_12 weeks_aerobic exercise vs. control**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

SF-36 Body Pain_12 weeks_aerobic exercise vs. yoga

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

SF-36 Limited activity following emotional problems_12 weeks_aerobic exercise vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

SF-36 Limited activity following emotional problems_12 weeks_aerobic exercise vs. yoga

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

SF-36 Limited activity following physical problems_12 weeks_aerobic exercise vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

SF-36 Limited activity following physical problems_12 weeks_aerobic exercise vs. yoga

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

SF-36 General Health_12 weeks_aerobic exercise vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

SF-36 General Health_12 weeks_aerobic exercise vs. yoga

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Hughes, 2009

Bibliographic Reference	Hughes, Ciara M; Smyth, S; Lowe-Strong, Andrea S; Reflexology for the treatment of pain in people with multiple sclerosis: a double-blind randomised sham-controlled clinical trial; Multiple Sclerosis Journal; 2009; vol. 15 (no. 11); 1329-1338

Study arms

Reflexology (N = 35)

Sham (N = 36)

Outcomes

Reflexology vs sham for pain relief in MS

Outcome	Reflexology , , N = 35	Sham, , N = 36
VAS pain Median (IQR)	5 (1 to 7)	5 (2 to 8)

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

ReflexologyvsshamforpainreliefinMS-VASpain-MedianIQR-Reflexology -Sham

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Jensen, 2009

Bibliographic Reference	Jensen, M. P.; Barber, J.; Romano, J. M.; Molton, I. R.; Raichle, K. A.; Osborne, T. L.; Engel, J. M.; Stoelb, B. L.; Kraft, G. H.; Patterson, D. R.; A comparison of self-hypnosis versus progressive muscle relaxation in patients with multiple sclerosis and chronic pain; Int J Clin Exp Hypn; 2009; vol. 57 (no. 2); 198-221

Study details

Trial name / registration number	
Study location	USA
Study setting	
Study dates	Not reported

Sources of funding	Supported by grants from the National Institute of Health, Department of Education and National Center of Disability and Rehabilitation Research.
Inclusion criteria	Diagnosis of MS, at least 18 years old, reported chronic daily pain that was rated as being at least 4/10, on average, on a 0 to 10 numerical rating scale of intensity and indicated on the survey that they would be willing to be contacted about possible participation in future research studies.
Exclusion criteria	Evidence of severe psychopathology symptoms or psychosis on interview or endorsement of active suicidal ideation with intent within the past 6 months, score of 21 or greater on the Telephone Interview of Cognitive Status indicative of severe cognitive deficits that could potentially interfere with the focused attention required for hypnosis.
Recruitment / selection of participants	Participants were recruited from a previously completed survey study of pain in people with MS.
Intervention(s)	Self-hypnosis training sessions given by a clinician following which the participants were encouraged to practice the skills learned at home by listening to audio recordings of the sessions at least once a day and by using a cue to reexperience hypnosis and the relief it provides. Ten sessions were given in total. The first 2 sessions included 5 analgesia suggestions which were decreased pain unpleasantness, deep relaxation, sensory substitution. imagined anaesthesia and decreased pain sensation. In the remaining 8 sessions only decreased unpleasantness of any sensations and 1 additional suggestion based on the individual participants response were used.
Comparator	Ten sessions of progressive muscle relaxation were used which involved tightening and relaxing different muscles groups throughout the body. Audiotapes of some of the sessions were given to the participants and they were encouraged to practice on their own at least once a day.
Number of participants	22 (15 randomised to self-hypnosis training and 8 progressive muscle relaxation)
Duration of follow-up	3 months
Indirectness	No indirectness
Additional comments	ITT

Study arms

Self-hypnosis training (N = 15)

Progressive muscle relaxation (N = 7)

Outcomes

Study timepoints

- Baseline
- 3 month

Self-hypnosis training compared to progressive muscle training for pain in MS

Outcome	Self-hypnosis training, Baseline, N = 15	Self-hypnosis training, 3-month, N = 15	Progressive muscle relaxation , Baseline, N = 15	Progressive muscle relaxation , 3-month, N = 15
Daily pain intensity (NRS 0-10) Mean (SD)	4.55 (1.35)	3.48 (2.04)	4.08 (1.38)	3.35 (1.92)
Pain interference (modified BPI score) Mean (SD)	4.66 (1.87)	3.78 (2.13)	4.46 (3.25)	4.35 (3.17)

Daily pain intensity (NRS 0-10) - Polarity - Lower values are better
Pain interference (modified BPI score) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Daily pain intensity (NRS 0-10)_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Pain interference (modified BDI score)_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Jensen, 2018

Bibliographic Reference	Jensen, M. P.; Battalio, S. L.; Chan, J. F.; Edwards, K. A.; Day, M. A.; Sherlin, L. H.; Ehde, D. M.; USE OF NEUROFEEDBACK AND MINDFULNESS TO ENHANCE RESPONSE TO HYPNOSIS TREATMENT IN INDIVIDUALS WITH MULTIPLE SCLEROSIS: Results From a Pilot Randomized Clinical Trial; International Journal of Clinical & Experimental Hypnosis; 2018; vol. 66 (no. 3); 231-264

Study details

Other publications associated with this study included in review	
Trial name / registration number	
Study dates	Participants were recruited between June 2015 and August 2016
Sources of funding	

Inclusion criteria	18 years or older, >= 6 months post-MS diagnosis, otherwise healthy, daily pain related to their MS that has been present for at least 6 months,average MS pain intensity over the past week of at least 4 on a 0 to 10 numerical rating scale, and able to read, write, and understand English.
Exclusion criteria	history of a seizure disorder, significant psychological or psychiatric disturbance, intermittent pain, hospitalisation or psychiatric reasons in the past 6 months, or failure to pass a cognitive screening test and experiencing an MS exacerbation.
Recruitment / selection of participants	Recruited from former participants of an ongoing MS symptom self-management study (who did not receive intervention), University of Washington Medical Center (UWMC) MS Clinic, Harborview and/or UWMC Rehabilitation Clinic and self-referrals from study brochures and flyers.
Intervention(s)	Self-hypnosis training + neurofeedback Six sessions (over 3 weeks) of theta-enhancing neurofeedback training (individually provided in person in the clinic), followed by single face-to-face hypnosis session and then 4 sessions of neurofeedback just before 4 audiotaped additional self-hypnosis training. Self-hypnosis training + mindfulness meditation Six sessions (over 3 weeks) of mindfulness training, followed by single face-to-face hypnosis session just before and then 4 sessions of mindfulness just before 4 audiotaped additional self-hypnosis training.
Population subgroups	
Comparator	Self-hypnosis training only Three weeks waiting period followed by a single face-to-face hypnosis session and then 4 audiotaped additional self-hypnosis training.
Number of participants	33 randomised; 12 Hypnosis + neurofedback, 12 Hypnosis+ meditation, 11 hypnosis only

Duration of follow-up	1 month
Indirectness	No indirectness
Additional comments	Per protocol

Study arms

Self-hypnosis training + neurofeedback (N = 12)

Self-hypnosis training+ mindfulness meditation (N = 12)

Control - Self-hypnosis training alone (N = 11)

Characteristics

Study-level characteristics

Characteristic	Study (N =)
% Female Sample size	n = 24 ; % = 75
Mean age (SD) (years) Mean (SD)	57.53 (10.62)
Relapsing-remitting Sample size	n = 17 ; % = 53
Secondary-progressive	n = 6 ; % = 19

Characteristic	Study (N =)
Sample size	
Primary-progressive Sample size	n = 3 ; % = 9
Progressive-relapsing Sample size	n = 0 ; % = 0
Uncertain Sample size	n = 6 ; % = 19
Years since diagnosis Mean (SD)	20.09 (15.08)
Duration of pain (years) Mean (SD)	20.91 (13.75)

Outcomes

Study timepoints

- Baseline
- 1 month

1 **Self-hypnosis, neurofeedback or mindfulness for pain in MS**

Outcome	Self-hypnosis training + neurofeedback, Baseline, N = 12	Self-hypnosis training + neurofeedback, 1 month, N = 12	Self-hypnosis training+ mindfulness meditation, Baseline, N = 12	Self-hypnosis training+ mindfulness meditation, 1 month, N = 12	Control - Self-hypnosis training alone, Baseline, N = 11	Control - Self-hypnosis training alone, 1 month, N = 11
Pain intensity (NRS 0-10) Mean (SD)	3.36 (1.17)	2.42 (1.23)	3.78 (1.35)	3.31 (1.28)	5.3 (1.57)	4.48 (2.17)
Sleep disturbance Mean (SD)	55.67 (6.72)	50.23 (5.23)	54.85 (9.62)	55.92 (11.61)	52.54 (10.12)	52.84 (10.94)
Pain interference (BPI) Mean (SD)	2.76 (1.2)	2.02 (1.53)	3.57 (2.5)	3.43 (1.09)	5.63 (1.57)	4.69 (2.99)
Pain catastrophising (PCS) Mean (SD)	11 (6.72)	9.17 (7.05)	14.75 (12.37)	12 (6.83)	17.2 (11.17)	14.8 (13.59)
Pain acceptance (CPAQ) Mean (SD)	79.17 (20.88)	82.67 (15.55)	73.5 (17.69)	74 (10.8)	66.4 (16.83)	72.4 (14.93)
Depression (PHQ-9 8-item) Patient Health	8.83 (3.86)	6.83 (2.62)	8.3 (4.81)	7.1 (3.7)	7.8 (4.59)	8.2 (6.18)

Outcome	Self-hypnosis training + neurofeedback, Baseline, N = 12	Self-hypnosis training + neurofeedback, 1 month, N = 12	Self-hypnosis training+ mindfulness meditation, Baseline, N = 12	Self-hypnosis training+ mindfulness meditation, 1 month, N = 12	Control - Self-hypnosis training alone, Baseline, N = 11	Control - Self-hypnosis training alone, 1 month, N = 11
Questionnaire. Scale likely 0-24. Mean (SD)						

Pain intensity (NRS 0-10) - Polarity - Lower values are better
Sleep disturbance - Polarity - Lower values are better
Pain interference (BPI) - Polarity - Lower values are better
Pain catastrophising (PCS) - Polarity - Lower values are better
Pain acceptance (CPAQ) - Polarity - Higher values are better
Depression (PHQ-9 8-item) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Pain intensity (NRS 0-10)_1 month_hypnosis + neurofeedback vs. hypnosis alone

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Pain intensity (NRS 0-10)_1 month_hypnosis + neurofeedback vs. hypnosis + mindfulness

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Pain intensity (NRS 0-10)_1 month_hypnosis + mindfulness vs. hypnosis alone

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Sleep disturbance_1 month_hypnosis + neurofeedback vs. hypnosis alone

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Sleep disturbance_1 month_hypnosis + neurofeedback vs. hypnosis + mindfulness

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Sleep disturbance_1 month_hypnosis + mindfulness vs. hypnosis alone

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Pain interference (BPI)_1 month_hypnosis + neurofeedback vs. hypnosis alone

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Pain interference (BPI)_1 month_hypnosis + neurofeedback vs. hypnosis + mindfulness

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Pain interference (BPI)_1 month_hypnosis + mindfulness vs. hypnosis alone

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Pain catastrophising_1 month_hypnosis + neurofeedback vs. hypnosis alone

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Pain catastrophising_1 month_hypnosis + neurofeedback vs. hypnosis + mindfulness

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **Pain catastrophising_1 month_hypnosis + mindfulness vs. hypnosis alone**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Pain acceptance (CPAQ)_1 month_hypnosis + neurofeedback vs. hypnosis alone**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Pain acceptance (CPAQ)_1 month_hypnosis + neurofeedback vs. hypnosis + mindfulness

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Pain acceptance (CPAQ)_1 month_mindfulness + neurofeedback vs. hypnosis alone

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Masoudi, 2013

Bibliographic Reference	Masoudi, R.; Sharifi Faradonbeh, A.; Mobasheri, M.; Moghadasi, J.; Evaluating the effectiveness of using a progressive muscle relaxation technique in reducing the pain of multiple sclerosis patients; Journal of musculoskeletal pain; 2013; vol. 21 (no. 4); 350-357

Study details

Trial name / registration number	IRCT138903182861N7

Study location	Iran
Sources of funding	Financial assistance from Shahrekord University of Medical sciences
Inclusion criteria	Not stated
Exclusion criteria	Those who had mental disorders, cognitive disorders, past history of drug addiction and other neurologic disorders
Recruitment / selection of participants	MS patients who were referred to the Department of Internal Neurology at Kashani Hospital, Sharrekord
Intervention(s)	An educational package was initially implemented. This included explaining the different muscles and muscle groups involved in the techniques, participants implementing the techniques in the presence of a researcher and predicting what participants might feel physically and mentally after implementation. Patients were then instructed to practice the techniques at home, once every day over a 3-month period with the help of an instructional CD. The exercises involved tensing and relaxing different muscle groups, breathing deeply and effectively at the same time.
Comparator	Participants were introduced to a relaxation technique in a single session and each subject received a cassette tape.
Duration of follow-up	3 months
Indirectness	No indirectness
Additional comments	ITT

Study arms

Progressive Muscle relaxation (PMRT) (N = 35)

Control (N = 35)
No intervention

Characteristics

Arm-level characteristics

Characteristic	Progressive Muscle relaxation (PMRT) (N = 35)	Control (N = 35)
% Female Sample size	n = 22	n = 23
20-30 years Sample size	n = 18	n = 20
31-40 years Sample size	n = 17	n = 15

Outcomes

Study timepoints

- Baseline
- 3 month

Progressive muscle relaxation for pain relief in MS

Outcome	Progressive Muscle relaxation (PMRT), Baseline, N = 35	Progressive Muscle relaxation (PMRT), 3-month, N = 35	Control, Baseline, N = 35	Control, 3-month, N = 35
Pain (VAS 0-10)	8.02 (1.7)	3.97 (1.72)	7.94 (1.28)	8.14 (0.94)

Outcome	Progressive Muscle relaxation (PMRT), Baseline, N = 35	Progressive Muscle relaxation (PMRT), 3-month, N = 35	Control, Baseline, N = 35	Control, 3-month, N = 35
Mean (SD)				

Pain (VAS 0-10) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Pain VAS (0-10)_3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Nazari, 2016

Bibliographic Reference	Nazari, F.; Soheili, M.; Hosseini, S.; Shaygannejad, V.; A comparison of the effects of reflexology and relaxation on pain in women with multiple sclerosis; Journal of Complementary & Integrative Medicine; 2016; vol. 13 (no. 1); 65-71

Study details

Trial name / registration number	3920940
Study location	Iran
Study setting	Community
Study dates	2013
Sources of funding	Isfahan University of Medical Sciences, Isfahan, Iran
Inclusion criteria	Women aged 18–50 years; had types of MS (relapsing-remitting, primary progressive, and secondary progressive), diagnosed by neurologists based on Mc Donald's criteria with the elapse of at least 6 months from relevant diagnosis; had willingness to participate in the research; and had healthy feet without deformity, callus or corn, cleft, active thrombosis or phlebitis, varicose veins, recent ankle trauma, sprain, fracture, inflammation, or infection. Other inclusion criteria for the study participants were: No previous participation in treatment sessions such as reflexology, relaxation, or massage in the last 6 months; having fatigue severity score of equal to and over 4 based on fatigue severity scale (FSS) and having scores 0–5.5 based on the Expanded Disability Status Scale (EDSS); not being in the menstruation period; not afflicted with diseases other than MS, such as febrile acute or chronic mental or psychic disorders such as severe depression, speech or hearing disorder; not addicted to narcotics and psychotropic drugs; not being a member of the treatment crew (physician or nurse); and not being pregnant.
Exclusion criteria	Not willing to continue in the research; use of other types of complementary and alternative medicine methods; disability to participate in the sessions (over two consecutive absences in the reflexology and relaxation meetings); and disease recurrence within 1 month before the start of the interventions and/or during the intervention, which caused hospitalisation.

Recruitment / selection of participants	Patients with MS referring to Ayatollah Kashani Hospital MS Clinic affiliated to Isfahan University of Medical Sciences
Intervention(s)	For the experimental groups, the interventions of reflexology and relaxation were performed for 4 weeks, twice a week for 40 min in each session. The intervention technique for the relaxation group was the combination of Jacobson and Benson applied upon full description on the intervention using the relaxation method with a CD which had been previously recorded and prepared, in which the research subjects were encouraged to perform the instructions. They should contract the muscles of each part of their body in an orderly manner for 5 s and then maintain them for 15 s in full relaxation state. Afterward, through mental conceptualization and application of all their senses, creative visualization, and concentration and respiration, relaxation was completed. In the reflexology group, upon full description of the intervention, first of all, a general reflex therapy was performed by massaging all plantar reflexology points and then, a special reflex therapy was done. The major reflexive points in the feet were put under pressure using the thumb and index finger. Finally, the intervention was completed by the researcher with massage of the solar plexus.
Comparator	The control group received only routine treatment and care recommended by the attending physician
Number of participants	75 randomised across the 3 groups; 25 reflexology, 25 relaxation, 25 control
Duration of follow-up	2 months
Indirectness	No indirectness
Additional comments	

1

Study arms

Relaxation (N = 25)

Reflexology (N = 25)

Control (N = 25)

Characteristics

Study-level characteristics

Characteristic	Study (N = 75)
% Female Sample size	n = 75 ; % = 100

Arm-level characteristics

Characteristic	Relaxation (N = 25)	Reflexology (N = 25)	Control (N = 25)
Mean age (SD) Mean (SD)	33.9 (5.6)	34.4 (6.6)	34.4 (7.7)
Duration of MS (years) Mean (SD)	6.66 (5.47)	5.18 (4.69)	4.78 (3.36)

Outcomes

Study timepoints

- Baseline

- 2 month

Relaxation compared to reflexology and control for pain relief in MS

Outcome	Relaxation , Baseline, N = 25	Relaxation , 2-month, N = 25	Reflexology, Baseline, N = 25	Reflexology, 2-month, N = 25	Control, Baseline, N = 25	Control, 2-month, N = 25
Pain (NRS) Mean (SD)	5.76 (1.64)	5.16 (1.68)	5.72 (1.96)	4.64 (2.11)	5.88 (1.83)	5.32 (1.72)

Pain (NRS) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Pain (NRS)_2 months_relaxation vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Pain (NRS)_2 months_reflexology vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Pain (NRS)_2 months_relaxation vs. reflexology

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Negahban, 2013

Bibliographic Reference	Negahban, H.; Rezaie, S.; Goharpey, S.; Massage therapy and exercise therapy in patients with multiple sclerosis: a randomized controlled pilot study; Clinical Rehabilitation; 2013; vol. 27 (no. 12); 1126-36

Study details

Secondary publication of another included study- see primary study for details	
Study location	Iran

Study setting	
Study dates	Not reported
Sources of funding	supported by a Masters thesis grant (no: PHT-9111) in Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
Inclusion criteria	Patients were included in the study if they had clinically or laboratory confirmed relapsing–remitting or secondary progressive multiple sclerosis an Expanded Disability Status Scale18 between 2 and 6, ability to stand unassisted for at least 60 seconds (using aids if required), and ability to walk 10 m safely even with an assistive device
Exclusion criteria	Severe relapse one month before the study; involvement in any physical therapy programme before beginning the study; unstable cardiovascular condition; diabetes; or lower limb arthritis that might interfere with the patient's participation in the prescribed intervention. Also, patients with any musculoskeletal or neurological conditions except multiple sclerosis were excluded.
Recruitment / selection of participants	Recruitment was performed by telephone contact after extracting the information provided in the medical records of the patients in the local Multiple Sclerosis Society.
Intervention(s)	**Massage alone** Three 30 min supervised intervention sessions per week for 5 weeks Swedish massage by trained massage therapist. **Exercise alone** Combined set of strength, stretch, endurance and balance training exercises including straight leg raising, forward lunge, hip adductor and calf muscles stretching, walking on a treadmill, cycling and balance board training **Massage + exercise**

	Three 30 min supervised intervention sessions per week for 5 weeks. Passive massage for 15 min and encouraged to perform active exercises of those included in the exercise therapy group. Time split between the two so that it did not exceed 30 min.
Comparator	Routine treatment and care recommended by attending physician and avoid participation in any exercise programme or change in their normal activities during the next five weeks. .
Number of participants	48 randomised to 4 equal groups: 12 massage, 12 relaxation, 12 massage
Duration of follow-up	5 weeks
Indirectness	No indirectness
Additional comments	ITT

Study arms

Massage therapy (N = 12)

Exercise therapy (N = 12)

Massage + Exercise combined (N = 12)

Control (N = 12)

Characteristics

Arm-level characteristics

Characteristic	Massage therapy (N = 12)	Exercise therapy (N = 12)	Massage + Exercise combined (N = 12)	Control (N = 12)
% Female Sample size	n = 10 ; % = 83	n = 10 ; % = 83	n = 10 ; % = 83	n = 10 ; % = 83
Mean age (SD) Mean (SD)	36.33 (7.62)	36.67 (6.69)	36.67 (7.63)	36.83 (8.74)
EDSS Mean (SD)	3.75 (1.37)	3.5 (1.13)	3.75 (1.43)	3.83 (1.39)
Time since onset (Months) Mean (SD)	148.7 (97.11)	102 (81.6)	115.3 (78.28)	86.58 (34.33)

Outcomes

Study timepoints

- Baseline
- 5 week

Massage and/or exercise for pain relief in MS

Outcome	Massage therapy, Baseline, N = 12	Massage therapy, 5-week, N = 12	Exercise therapy, Baseline, N = 12	Exercise therapy, 5-week, N = 12	Massage + Exercise combined , Baseline, N = 12	Massage + Exercise combined , 5-week, N = 12	Control , Baseline, N = 12	Control , 5-week, N = 12
Pain (VAS 0-10) Mean (SD)	4.91 (2.02)	1.75 (1.95)	1.83 (1.85)	1.41 (1.24)	4.75 (1.54)	2.66 (1.61)	4.25 (2.56)	4.83 (2.69)

Pain (VAS 0-10) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Pain (VAS 0-10)_5 weeks_massage vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Pain (VAS 0-10)_5 weeks_massage + exercise vs. massage alone

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Pain (VAS 0-10)_5 weeks_massage + exercise vs. exercise alone

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Pain (VAS 0-10)_5 weeks_exercise vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Pain (VAS 0-10)_5 weeks_massage + exercise vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Palm, 2016

Bibliographic Reference	Palm, U.; Chalah, M. A.; Padberg, F.; Al-Ani, T.; Abdellaoui, M.; Sorel, M.; Dimitri, D.; Creange, A.; Lefaucheur, J. P.; Ayache, S. S.; Effects of transcranial random noise stimulation (tRNS) on affect, pain and attention in multiple sclerosis; Restorative Neurology & Neuroscience; 2016; vol. 34 (no. 2); 189-99

Study details

Trial name / registration number	DRKS00005296

Study location	France
Study setting	Inpatient/outpatient departments
Sources of funding	One author reported to have received grants from neuroConn GmbH, Ilmenau, Germany
Inclusion criteria	aged 18-70 years; right handed as per Edinburgh inventory; definite MS diagnosis according to 2010 McDonald Criteria; presence of neuropathic pain based on NPSI for more than three months with intensity >40 on VAS performed daily for a representative week; stable pharmacological and physical therapies for at least a month; presence of measurable pain related evoked potentials at the right hand; absence of MS relapses within last 2 months; and absence of other neurological or psychiatric diseases.
Exclusion criteria	unable to perform Attention Network Test (including those with deficits in visual fields or severe upper limb impairment based on a Medical Research Council scale score <12 (scale for muscle power applied to four muscle groups, with scores ranging between 0 and 20, with 20 indicating full strength).
Recruitment / selection of participants	Recruited from inpatient and outpatient Neurology departments at a single hospital in France
Intervention(s)	Transcranial random noise stimulation (tRNS): applied by STARSTIM device with saline-soaked sponges mounted on an adult-sized cap worn by patients with pre-defined localisation of anode (F3) and cathode (AF8) according to 10-20 EEG system. Stimulation parameters: tRNS with DC-offset applied for 20 min over 3 days, with offset programmed at 1 mA to avoid negative polarisation. Variance of stimulation set to 650/2 microA (indicating two-tailed SD of 325 microA and peak to peak amplitude of 2 mA. White noise applied in full band from 0 to 500 Hz, including mostly excitatory frequencies from 100 Hz upwards (exclusion of 0-100 Hz not supported by device). Randomly received two blocks of tRNS (active or sham) consisting each of three consecutive daily sessions separated by a three-week washout period. Well-trained physician performed the stimulations in an illuminated and quiet room with patients resting.
Comparator	Sham tRNS: applied by STARSTIM device as for intervention but for sham stimulation the STARSTIM software sham stimulation mode was used, with current switched off automatically after a ramp-in of 15 sec tRNS. Randomly received two blocks of tRNS (active or sham) consisting each of three consecutive daily sessions separated by a three-week washout period. Well-trained physician performed the stimulations in an illuminated and quiet room with patients resting.
Number of participants	16

Duration of follow-up	4 weeks

Study arms

Transcranial Noise Stimulation (tRNS) (N = 8)

Sham (N = 8)

Characteristics

Study-level characteristics

Characteristic	Study (N = 16)
% Female Sample size	n = 13 ; % = 81.3
Mean age (SD) Mean (SD)	47.4 (8.9)
Relapsing remitting Sample size	n = 11 ; % = 68.8
Primary progressive Sample size	n = 1 ; % = 6.3

Outcomes

Study timepoints

- Baseline
- 4 week

tRNS compared to sham for pain relief in MS

Outcome	Transcranial Noise Stimulation (tRNS), Baseline, N = 8	Transcranial Noise Stimulation (tRNS), 4-week, N = 8	Sham, Baseline, N = 8	Sham, 4-week, N = 8
VAS (0-100) Mean (SD)	50.1 (22.5)	47.2 (16.7)	51.1 (19.6)	50.3 (19.7)
HADS total score Mean (SD)	NR (NR)	NR (NR)	14.4 (5.9)	14.5 (6.5)
BPI Global score Mean (SD)	9.4 (2.8)	8.6 (3.1)	9.9 (3.5)	9.2 (3.1)

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Cross-over trial
VAS (0-100)_4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1

2 **BPI global score_4 weeks**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

3

1 **Pilutti, 2014**

Bibliographic Reference	Pilutti, L. A.; Dlugonski, D.; Sandroff, B. M.; Klaren, R.; Motl, R. W.; Randomized controlled trial of a behavioural intervention targeting symptoms and physical activity in multiple sclerosis; Multiple Sclerosis; 2014; vol. 20 (no. 5); 594-601

2

3 ## Study details

Study location	USA
Study setting	Community
Study dates	Not reported
Sources of funding	Supported, in part, by a grant from the National Multiple Sclerosis Society [PP1695]. One of the authors was the recipient of a Postdoctoral Fellowship from the Multiple Sclerosis Society of Canada and a Du Pré Grant from the Multiple Sclerosis International Federation.
Inclusion criteria	18–64 years; diagnosis of MS; relapse-free for the past 30 days; Internet access; and ability to walk with or without an assistive device. Participants further provided physician's approval for participation, were willing and able to travel to the research site, and had minimal risk for engaging in physical activity (i.e., reported 'yes' to less than two questions on the Physical Activity Readiness Questionnaire).
Exclusion criteria	participants who self-reported accumulating ≥30 minutes of moderate-to-vigorous physical activity (MVPA) per day on ≥2 days/week.
Recruitment / selection of participants	A flyer with study information and eligibility criteria was mailed to patients in the North American Research Committee on Multiple Sclerosis (NARCOMS) database who resided in the local area and to participants from previous studies who had expressed interest in future research opportunities.
Intervention(s)	The goal of the behavioural intervention was to increase lifestyle physical activity, primarily walking, over a 6-month period. The behavioural intervention included several components, namely a dedicated study website with information about becoming more physically active based on principles of SCT, self-monitoring and goalsetting using a pedometer and activity logs, and one-on-one web-based video coaching sessions. The website content has been described in detail previously.12,13 New content became available seven times during the first 2 months, four times during the second 2 months, and twice during the final 2 months. Participants were encouraged to wear a pedometer daily for the entire 6 months. Participants recorded pedometer steps in a logbook at the end of each day and then entered and uploaded these steps to the study website using Goal Tracker, a program designed specifically for this study. This Goal

	Tracker program allowed participants to record steps, set a step count goal, and monitor progress towards this goal. There were 15 web-based video coaching sessions scheduled with one of three behavioural coaches, with seven occurring in the first 2 months, six in the second 2 months, and only two in the final 2 months. The behavioural coaches were highly trained doctoral students or a postdoctoral fellow, and followed the principles of supportive accountability as per TeleCoach guidelines
Comparator	Waitlist
Number of participants	82 randomised; 41 behavioural programme and 41 waitlist
Duration of follow-up	6 months
Indirectness	No indirectness

Study arms

Internet-delivered behavioural intervention (N = 41)

Intervention designed to increase lifestyle physical activity

Control (N = 41)

Characteristics

Arm-level characteristics

Characteristic	Internet-delivered behavioural intervention (N = 41)	Control (N = 41)
% Female Sample size	n = 30 ; % = 73	n = 32 ; % = 78
Mean age (SD) Mean (SD)	48.4 (9.1)	49.5 (9.2)

Characteristic	Internet-delivered behavioural intervention (N = 41)	Control (N = 41)
Relapsing-remitting Sample size	n = 31 ; % = 76	n = 34 ; % = 83
Secondary-progressive Sample size	n = 8 ; % = 19.5	n = 2 ; % = 4.9
Primary-progressive Sample size	n = 2 ; % = 4.9	n = 5 ; % = 12
HADS - depression Mean (SD)	6.3 (4.1)	6.3 (4)
HADS-anxiety Mean (SD)	5.5 (4.2)	5.5 (3.3)
MSIS physical Mean (SD)	28.6 (25.1)	34.5 (24.5)
MSIS psychological Mean (SD)	27.2 (21.4)	33.7 (23.4)

Outcomes

Study timepoints

- Baseline
- 6 month

Behavioural intervention for pain relief in MS

Outcome	Internet-delivered behavioural intervention , Baseline, N = 41	Internet-delivered behavioural intervention , 6-month, N = 37	Control, Baseline, N = 41	Control, 6-month, N = 39
HADS - depression Mean (SD)	6.3 (4.1)	5 (2.43)	6.3 (4)	6.6 (2.5)
HADS - anxiety Mean (SD)	5.5 (4.2)	4.1 (2.43)	5.5 (3.3)	5.6 (2.5)
SF-MPQ Mean (SD)	8.3 (7)	8.1 (4.26)	10.6 (7.7)	9.8 (3.75)
PSQI - Global Sleep Disturbance Mean (SD)	6.9 (4.1)	6.4 (2.43)	8.4 (4.3)	7.4 (2.45)
MSIS-29 Physical Mean (SD)	28.6 (25.1)	29.1 (9.12)	34.5 (24.5)	33.2 (9.36)
MSIS-29 Psychological Mean (SD)	27.2 (21.4)	27.6 (14.6)	33.7 (23.4)	33.1 (14.4)

HADS - depression - Polarity - Lower values are better
HADS - anxiety - Polarity - Lower values are better
SF-MPQ - Polarity - Lower values are better
PSQI - Global Sleep Disturbance - Polarity - Lower values are better
MSIS-29 Physical - Polarity - Lower values are better
MSIS-29 Psychological - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

HADS depression_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

HADS anxiety_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

SF-MPQ-6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

1 **PSQI - Global Sleep Disturbance_6 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **MSIS-29 physical_6 months**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

MSIS-29 psychological_6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Young, 2019

Bibliographic Reference	Young, H. J.; Mehta, T. S.; Herman, C.; Wang, F.; Rimmer, J. H.; The Effects of M2M and Adapted Yoga on Physical and Psychosocial Outcomes in People With Multiple Sclerosis; Archives of Physical Medicine & Rehabilitation; 2019; vol. 100 (no. 3); 391-400

Study details

Trial name / registration number	NCT02533882.
Study location	USA
Study setting	Outpatient
Study dates	Recruited between December 2014 and August 2016
Sources of funding	Supported by the National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR grant no. 90DP0059-01-00). NIDILRR is a centre within the Administration for Community Living (ACL), Department of Health and Human Services (HHS).
Inclusion criteria	self-reported a diagnosis of MS, with a Patient Determined Disease Steps score between 0 and 6; aged 18- 65 years; ability to exercise with arms and/or legs; and physician clearance
Exclusion criteria	Participation in a similar intervention in the last 6 months; use of tobacco products in the last 6 months; unstable weight; cognitive impairment (MiniMental State Exam score <24); active pressure ulcer; and any contraindications to exercise based on the American College of Sports Medicine guidelines
Recruitment / selection of participants	Potential participants were identified from the membership database of a community-based health and fitness facility for individuals with physical disabilities, physician referrals, flyers, informational mailings, and word of mouth between December 2014 and August 2016
Intervention(s)	Movement to music: combinations of movement forms that were structured to target strength, cardiorespiratory endurance and balance. Each class was choreographed by an experienced dance instructor and incorporated multiple movement routines accompanied with music. Every routine specifically targeted a fitness component, with the movements and tempo adapted to participants' functional level. For example, standing routines were adapted to seated versions for participants who experienced excessive fatigue during prolonged standing. Each class started with warm-

	up focusing on upper and lower extremity range of motions in a seated position, followed by upper extremity muscle strengthening, cardiorespiratory endurance, lower extremity muscle strengthening, and balance routines performed either seated or standing with or without support of a dance barre. The class ended with a cool-down routine that emphasized breathing and mindfulness. Equipment included chairs, wrist weights, TheraBands, exercise balls, and ribbons. Three 60-minute exercise sessions per week for 12 weeks. Adapted yoga: taught by yoga instructors that were YogaFit level 1 certified and had experience adapting yoga to people with disabilities. Delivered in Iyengar approach to Hatha yoga. Series of stationary poses using isometric contraction and relaxation techniques to obtain specific body alignments. Performed either seated or standing. Based on 3-Mountain format including warm-up phase, work phase and cool-down phase. Progressively introducing new and advanced poses. Adapted for those with limited flexibility and/or strength by using props (e.g., chairs/straps) to help with poses. Each class ended with relaxation. Three 60-minute exercise sessions per week for 12 weeks.
Population subgroups	None
Comparator	Waitlist control: received biweekly newsletters that provided educational information on living with MS. Information was obtained through the National Center on Health, Physical Activity and Disability. Participants were instructed to maintain usual activities.
Number of participants	81 randomised, all appear to be analysed despite loss to follow-up (n=61 were not lost to follow-up)
Duration of follow-up	3 months - end of intervention
Indirectness	None

Study arms

Movement to Music (M2M) (N = 27)

Adapted Yoga (N = 26)

Waitlist control (N = 28)

Characteristics

Arm-level characteristics

Characteristic	Movement to Music (M2M) (N = 27)	Adapted Yoga (N = 26)	Waitlist control (N = 28)
% Female Sample size	n = 22 ; % = 81.5	n = 20 ; % = 76.9	n = 24 ; % = 85.7
Mean age (SD) Calculated across the groups using RevMan calculator Mean (SD)	49.67 (9.4)	48.35 (9.95)	47.29 (10.33)
MS duration (years) Mean (SD)	13.56 (8.26)	10.98 (5.57)	13.38 (8.5)
PDDS score Mean (SD)	2.37 (2.13)	1.58 (1.9)	2.57 (2.01)

Outcomes

Study timepoints

- Baseline
- 12 week (Described in the study as: outcomes reported in the last 7 days)

M2M and Adapted Yoga for pain relief in MS

Outcome	Movement to Music (M2M), Baseline, N = 27	Movement to Music (M2M), 12-week, N = 27	Adapted Yoga, Baseline, N = 26	Adapted Yoga, 12-week, N = 26	Waitlist control , Baseline, N = 28	Waitlist control , 12-week, N = 28
Pain Interference (PROMIS Interference Short Form 8a)) Mean (SD)	52.3 (9.7)	53.1 (10.4)	52.7 (9.1)	53.3 (8.1)	52.9 (9.8)	51.7 (9)

Pain Interference (PROMIS Interference Short Form 8a)) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Pain interference (PROMIS interference short form 8a)_12 weeks_movement to music vs. adapted yoga

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Pain interference (PROMIS interference short form 8a)_12 weeks_adapted yoga vs. waitlist control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Pain interference (PROMIS interference short form 8a)_12 weeks_movement to music vs. waitlist control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Young, 2020

Bibliographic Reference	Young, J.; Zoghi, M.; Khan, F.; Galea, M. P.; The Effect of Transcranial Direct Current Stimulation on Chronic Neuropathic Pain in Patients with Multiple Sclerosis: Randomized Controlled Trial; Pain Medicine; 2020; vol. 21 (no. 12); 3451-3457

Study details

Secondary publication of another included study- see primary study for details	

Other publications associated with this study included in review	
Trial name / registration number	Not stated
Study location	Australia
Study setting	Clinic room in a hospital environment
Study dates	Not stated
Sources of funding	
Inclusion criteria	18 years and over with a diagnosis of MS based on the McDonald criteria. Level of pain on at least 4 on VAS. Central pain defined as pain consistent with a central nervous system lesion. all previous treatments with various medications for pain management stable for at least 2 months before treatment. No other nociceptive and peripheral neuropathic pain, psychiatric disease, headache or optic neuritis. Able to understand English.
Exclusion criteria	Patients experiencing an acute exacerbation of MS. Had a skin condition on the scalp, existing metal in the head, existing implanted devices. Patients who suffered frequent or severe headaches, were pregnant or breastfeeding.
Recruitment / selection of participants	Recruitment from inpatients and outpatients of the Royal Melbourne Hospital, a tertiary hospital in Melbourne.
Intervention(s)	A constant current of 2mA was applied for 10 minutes stimulation, 25 minutes of non-stimulation and then another 10 minutes of stimulation at approximately the same time for 5 consecutive days

Population subgroups	
Comparator	Sham tDCS using the same set up as intervention group but stimulation was turned on for 30 seconds then ramped down to no stimulation.
Duration of follow-up	4 weeks
Additional comments	ITT

Study arms

Anodal tDCS (N = 15)

Sham (N = 15)

Characteristics

Arm-level characteristics

Characteristic	Anodal tDCS (N = 15)	Sham (N = 15)
% Female Sample size	n = 11 ; % = 73.3	n = 13 ; % = 86
Mean age (SD) Mean (SD)	51.2 (9.3)	49.87 (12.9)
Relapsing-remitting MS Sample size	n = 9 ; % = 60	n = 7 ; % = 46.7
Primary-progressive MS	n = 1 ; % = 6.7	n = 2 ; % = 13

Characteristic	Anodal tDCS (N = 15)	Sham (N = 15)
Sample size		
Secondary-progressive MS Sample size	n = 5 ; % = 33.3	n = 6 ; % = 40

Outcomes

Study timepoints

- Baseline
- 4 week

Anodal tDCS compared to sham for pain relief in MS

Outcome	Anodal tDCS, Baseline, N = 15	Anodal tDCS, 4-week, N = 15	Sham, Baseline, N = 15	Sham, 4-week, N = 15
VAS Mean (SD)	6.3 (2)	3.7 (3)	5.8 (2)	5.3 (3)
Neuropathic Pain Scale (NPS) Mean (SD)	45.5 (17)	38.9 (25)	51.8 (16)	44.6 (23)
MSQOL-54 Physical Mean (SD)	47.9 (18)	52.5 (19)	38.8 (19)	39.6 (18)
MSQOL-54 Mental Mean (SD)	68.3 (18)	70.2 (14)	53.2 (21)	53.3 (21)

Outcome	Anodal tDCS, Baseline, N = 15	Anodal tDCS, 4-week, N = 15	Sham, Baseline, N = 15	Sham, 4-week, N = 15
DASS-Depression Mean (SD)	6.9 (9.6)	6.6 (6.2)	12.8 (10)	12.5 (12)
DASS-Anxiety Mean (SD)	7.9 (7)	7.1 (7)	12.1 (8)	11.7 (10)

VAS - Polarity - Lower values are better
MSQOL-54 Physical - Polarity - Higher values are better
MSQOL-54 Mental - Polarity - Higher values are better
DASS-Depression - Polarity - Lower values are better
DASS-Anxiety - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
VAS_4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Neuropathic Pain Scale_4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

MSQOL-54 Physical_4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

DASS Depression_4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

DASS Anxiety_4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

D.2 Evidence tables for studies included in the previous guideline

Table 33: Al-Smadi 2003

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
Al-Smadi J et al. A pilot investigation of the hypoalgesic effects of transcutaneous electrical nerve stimulation upon low back pain in people with multiple sclerosis. Clin Rehabil 2003; 17: 742-749.	Randomised double-blind placebo-controlled trial. Computer randomisation list generated, and allocation drawn up by member of the research team not involved in running the trial.	15 (5 in each group; all analysed)	Inclusion: Age 18 to 65 years; MS; stable low back pain (present at least 3 months and had not responded to conventional treatments); antispasticity and pain medication and physiotherapy stabilised for at least 30 days prior to recruitment Exclusion: other serious illness likely to interfere with the study; serious spinal pathology (red flags) and/or psychosocial risk factors (yellow flags); contraindication to TENS; not competent to give informed consent; analgesic abuse; sacral pressure ulcers; participating in other research studies currently or in previous 3 months Overall age 34-65 years (not shown by group) **TENS 1** / **TENS 2** / **Placebo TENS** VAS scores not shown at baseline	TENS 1 (4 Hz, 200µs) TENS 2 (110 Hz, 200µs)	Placebo TENS	Baseline, week 6 (end of treatment) and week 10 (4 week follow up)	Multiple Sclerosis Society of Great Britain and Northern Ireland

Reference	Study type	No. pts	Patient characteristics				Intervention	Comparison	Length of follow-up	Source of funding
ALSMADI2003	Blinded outcome assessment. Study underpowered. Differences between groups at baseline; change scores with SEM or SD for change score not shown; final scores should not be compared. Not all baseline or outcome data shown.		Leeds MS QOL	15.6 (0.9)	12.2 (2.7)	14.6 (2.2)				
			Roland Morris DQ	16.7 (1.0)	18.2 (1.8)	16.4 (1.4)				
			McGill PQ	42.6 (2.9)	21.4 (2.9)	30.6 (2.5)				
			SF-36 physical	81.4 (22.0)	88.8 (29.7)	115.2 (15.5)				
			SF-36 mental	182.5 (32.1)	146.0 (38.8)	146.6 (30.6)				
			NB Differences between groups at baseline							

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding

Results.

Week 6:	TENS 1	TENS 2	Placebo TENS	
VAS for current low back pain (decrease = improvement)	-22.7 (SEM 16.5) Not statistically significant	Not shown	Not shown	No difference between groups
Right leg pain (decrease = improvement)	-4.5 (SEM 3.5) Not statistically significant	Not shown	Not shown	No difference between groups
Left leg pain (decrease = improvement)	-13 (SEM 13.4) Not statistically significant	Not shown	Not shown	No difference between groups
Leeds Multiple Sclerosis Quality of Life Questionnaire (decrease = improvement)	8.4 (SEM 3.3) Significance not stated	10.6 (SEM 3.0) Significance not stated	13.2 (SEM 3.3) Significance not stated	No difference between groups
Roland Morris Disability Questionnaire (decrease = improvement)	10.2 (SEM 2.3) Not statistically significant	15.6 (SEM 1.9) Not statistically significant	15.0 (SEM 2.5) Not statistically significant	No difference between groups
McGill Pain Questionnaire (decrease = improvement)	33.0 (SEM 5.4)	22.2 (SEM 4.1)	32.4 (SEM 4.6)	No difference between groups

Reference	Study type	No. pts	Patient characteristics		Intervention	Comparison	Length of follow-up	Source of funding
			Significance not stated	Not statistically significant	Not statistically significant			
SF-36 physical component score (increase = improvement)			126 (SEM 27.5) Significance not stated	150 (SEM 25.6) Significance not stated	140.8 (SEM 46.5) Significance not stated	No difference between groups		
SF-36 mental component score (increase = improvement)			234.2 (SEM 43.2) Significance not stated	217.6 (SEM 43.2) Significance not stated	164 (SEM 67.9) Significance not stated	No difference between groups		
Week 10:			**TENS 1**	**TENS 2**	**Placebo TENS**			
VAS for current low back pain (decrease = improvement)			-23.6 (SEM 15.1) Not statistically significant	Not shown	Not shown	No difference between groups		
Right leg pain (decrease = improvement)			-37.6 (SEM 18.7) Not statistically significant	Not shown	Not shown	No difference between groups		
Left leg pain (decrease = improvement)			-20.2 (SEM 7.1) Not statistically significant	Not shown	Not shown	No difference between groups		
Leeds Multiple Sclerosis Quality of Life Questionnaire (decrease = improvement)			11.2 (SEM 3.1)	11.0 (SEM 1.6)	14.8 (SEM 2.4)	No difference between groups		

Reference	Study type	No. pts	Patient characteristics		Intervention	Comparison	Length of follow-up	Source of funding
			Significance not stated	Not statistically significant	Not statistically significant			
Roland Morris Disability Questionnaire (decrease = improvement)			14.2 (SEM 2.2) Not statistically significant	13.7 (SEM 2.9) Not statistically significant	17.0 (SEM 1.6) Not statistically significant	No difference between groups		
McGill Pain Questionnaire (decrease = improvement)			29.0 (SEM 5.0) Significance not stated	21.7 (SEM 5.1) Not statistically significant	30.8 (SEM 4.2) Not statistically significant	No difference between groups		
SF-36 physical component score (increase = improvement)			112.4 (SEM 36.8) Significance not stated	143.7 (SEM 9.0) Significance not stated	102.0 (SEM 40.7) Significance not stated	No difference between groups		
SF-36 mental component score (increase = improvement)			230.3 (SEM 41.6) Significance not stated	212.1 (SEM 46.6) Significance not stated	154.3 (SEM 38.0) Significance not stated	No difference between groups		

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1 **Table 34: Castro-Sanchez 2012**

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Source of funding
Castro-Sanchez AM et al. Hydrotherapy for the treatment of pain in people with multiple sclerosis: a randomized controlled trial. Evidence-Based Complementary and Alternative Medicine 2012; Article ID 473963	Randomised controlled trial. Selection of groups balanced for type of medication received; randomisation stratified by medication; computer generated list by blinded researcher; sealed envelopes. Power calculatio	73: Ai-Chi n=36; control n=37 (2 excluded during 20-week treatment period due to relapse)	Inclusion: MS patients; age 18 to 75 years; VAS pain score >4 for at least 2 months; EDSS ≤7.5. Exclusion: Treatment with another CAM currently or within previous 3 months; relapse requiring hospitalisation or steroid treatment in last 2 months			Ai-Chi aquatic exercise in swimming pool (36°C); 40 sessions (twice a week for 20 weeks); combination of deep breathing and slow broad movements of arms, legs and torso to work on balance, strength, relaxation, flexibility and breathing; with relaxing Tai-Chi music	Abdominal breathing and contraction-relaxation exercises in therapy room, supine on exercise mat; no music; 40 sessions (twice a week for 20 weeks)	Baseline, 20 weeks (end of treatment), 4 and 10 weeks follow up	Not stated
				Ai-Chi	Controls				
			Mean age	46 (9.97)	50 (12.31)				
			Gender	26 female/ 10 male	24 female/ 13 male				
			EDSS	6.3 (0.8)	5.9 (0.9)				

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Source of funding
CASTRO2012	n suggested minimal sample size of 33 per group for a power of 80% and SD 3.1. Blinded outcome assessment		Years since diagnosis	10.7 (9.1)	11.9 (8.7)				
			Type of MS: primary progressive secondary progressive not known	6 9 21	9 12 16				
			Mean pain VAS	8.3 (1.2)	7.8 (1.6)				
			All differences non-significant.						

Results.

Outcome measure Median (SD)	Group	Baseline	Week 20	Week 24	Week 30	% change from baseline to week 20
Pain VAS (0-10)	**Control** **Exp.**	7 (1.9) 7 (2.1)	6 (2.3) NS vs. baseline 3 (2.3) p<0.028 vs. baseline; p<0.044 vs. control	6 (2.1) NS vs. baseline 4 (2.6) p<0.035 vs. baseline; p<0.049 vs. control	6 (2.4) NS vs. baseline 5 (2.5) p<0.047 vs. baseline; NS vs. control	23% improvement 50% improvement

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
McGill Pain Questionnaire Pain Rating Index (PRI 0-77)	**Control** **Exp.**	23 (10.21) 19 (11.34)	20 (12.47) NS vs. baseline 12 (7.45) p<0.037 vs. baseline; p<0.044 vs. control	21 (11.53) NS vs. baseline 14 (10.04) p<0.043 vs. baseline; p<0.031 vs. control	22 (10.06) NS vs. baseline 19 (12.19) NS vs. baseline; NS vs. control	17% improvement 40% improvement	
McGill Pain Questionnaire Present Pain Intensity (PPI 0-5)	**Control** **Exp.**	2 (1.5) 2 (1.7)	2 (1.1) NS vs. baseline 1 (0.5) p<0.034 vs. baseline; NS vs. control	2 (1.4) NS vs. baseline 1 (1.5) NS vs. baseline; NS vs. control	2 (1.3) NS vs. baseline 2 (1.8) NS vs. baseline; NS vs. control	5% improvement 40% improvement	
Roland Morris Disability Questionnaire (0-24)	**Control** **Exp.**	9 (6.11) 7 (8.43)	5 (4.27) p<0.033 vs. baseline 2 (1.56); p<0.021 vs. baseline; p<0.044 vs. control	6 (5.33) p<0.048 vs. baseline 3 (2.32) p<0.026 vs. baseline; p<0.042 vs. control	8 (5.91) NS vs. baseline 3 (2.05) p<0.028 vs. baseline; p<0.027 vs. control	12% improvement 100% improvement	
Spasm VAS (0-10)	**Control** **Exp.**	6 (3.1) 5 (2.8)	4 (4.5) NS vs. baseline 2 (4.3) p<0.039 vs. baseline; p<0.048 vs. control	5 (3.86) NS vs. baseline 2 (3.9) p<0.040 vs. baseline; p<0.042 vs. control	6 (2.76) NS vs. baseline 4 (3.1) p<0.067 vs. week 20; NS vs. control	10% improvement 91% improvement	
Multiple Sclerosis Impact Scale (MSIS)-29 Physical (0-100)	**Control** **Exp.**	46 (18.34) 48 (15.91)	45 (17.14) NS vs. baseline 41 (12.37) p<0.013 vs. baseline; p<0.014 vs. control	46 (19.12) NS vs. baseline 45 (11.25) p<0.017 vs. baseline; p<0.019 vs. control	46 (15.93) NS vs. baseline 48 (12.89) p<0.025 vs. baseline; p<0.027 vs. control	6% improvement 78% improvement	

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
Multiple Sclerosis Impact Scale (MSIS)-29 Psychological (0-100)	**Control** **Exp.**	30 (23.53) 34 (29.47)	25 (19.36) p<0.046 vs. baseline 21 (15.73); p<0.009 vs. baseline; p<0.023 vs. control	27 (21.29) 22 (17.94) p<0.018 vs. baseline; p<0.027 vs. control	29 (20.39) 24 (11.27) p<0.024 vs. baseline; p<0.038 vs. control	37% improvement 81% improvement	
Modified Fatigue Impact Scale (MFIS) Physical (0-36)	**Control** **Exp.**	25 (9.41) 26 (9.02)	22 (11.03) NS vs. baseline 14 (10.37) p<0.032 vs. baseline; p<0.042 vs. control	23 (10.34) NS vs. baseline 17 (9.76) p<0.038 vs. baseline; p<0.044 vs. control	24 (11.17) NS vs. baseline 22 (13.81) NS vs. baseline; NS vs. control	9% improvement 48% improvement	
Modified Fatigue Impact Scale (MFIS) Cognitive (0-40)	**Control** **Exp.**	19 (8.95) 23 (9.82)	17 (7.13) NS vs. baseline 13 (3.41) p<0.038 vs. baseline; NS vs. control	17 (8.59) NS vs. baseline 15 (6.28) p<0.044 vs. baseline; NS vs. control	18 (10.27) NS vs. baseline 17 (7.95) NS vs. baseline; NS vs. control	13% improvement 61% improvement	
Modified Fatigue Impact Scale (MFIS) Psychological (0-40)	**Control** **Exp.**	5 (2.8) 5 (2.2)	4 (3.1) NS vs. baseline 2 (2.1) p<0.041 vs. baseline; NS vs. control	4 (2.9) NS vs. baseline 2 (1.3) p<0.038 vs. baseline; NS vs. control	5 (3.4) NS vs. baseline 3 (2.3) NS vs. baseline; NS vs. control	26% improvement 58% improvement	
Fatigue Severity Scale (1-7)	**Control** **Exp.**	5 (5.1) 6 (3.1)	4 (3.9) NS vs. baseline 3 (2.2) p<0.043 vs. baseline; NS vs. control	5 (5.2) NS vs. baseline 3 (2.4) p<0.046 vs. baseline; p<0.048 vs. control	5 (3.8) NS vs. baseline 4 (2.2); NS vs. baseline; NS vs. control	12% improvement 39% improvement	

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
Beck Depression Inventory (0-63)	**Control** **Exp.**	15 (8.68) 14 (7.72)	13 (5.91) NS vs. baseline 5 (3.2) p<0.028 vs. baseline; p<0.031 vs. control	14 (9.01) NS vs. baseline 9 (4.88) p<0.040 vs. baseline; p<0.039 vs. control	14 (8.93) NS vs. baseline 11 (5.92) NS vs. baseline; NS vs. control	11% improvement 52% improvement	
Barthel Index (0-100)	**Control** **Exp.**	87 (10.34) 91 (7.12)	88 (8.92) NS vs. baseline 86 (9.23) p<0.047 vs. baseline; NS vs. control	90 (7.65) NS vs. baseline 87 (8.79) p<0.049 vs. baseline; NS vs. control	90 (8.73) NS vs. baseline 89 (9.05) NS vs. baseline; NS vs. control	2% improvement 9% improvement	

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1 **Table 35: Hughes 2009**

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Source of funding
Hughes CM et al. Reflexology for the treatment of pain in people with multiple sclerosis: a double-blind randomised sham-controlled clinical trial. Mult Scler 2009; 15: 1329-1338. HUGHES 2009	Double-blind randomised controlled trial. Computer-generated randomisation list prepared by independent investigator with no other involvement in trial. Power calculation: 31	71: precision reflexology 35 + sham reflexology 36. During the 10 weeks of treatment, 2 participants in Sham group withdrew due to personal circumstances; 1 relapsed and 1 died (32 assessed at week 10). 1 further participant in Sham group relapsed prior to 22 week follow up (31 assessed at week 22).	Inclusion: Age 18 to 75 years; MS; pain >4 on VAS of at least 2 months' duration and EDSS ≤7.5 Exclusion: Previous experience of reflexology; participation in research study currently or in previous 3 months; relapse requiring hospitalisation or steroid treatment in past 2 months			Precision reflexology 45-minute sessions weekly for 10 weeks; stimulation of all the key reflex points on the feet associated with organs throughout the body	Sham reflexology 45-minute sessions weekly for 10 weeks; standardised foot massage with less pressure but avoiding the points representative of common areas of pain associated with MS.	Blinded assessment at baseline, week 10 (end of treatment) and weeks 16 and 22 (follow up)	National Multiple Sclerosis Society, USA
				Precision reflexology	Sham reflexology				
			Age	50 (11.1)	53 (11.0)				
			Gender	30 females/ 5 males	29 females/ 7 males				
			EDSS	5.8 (0.95)	6.2 (0.8)				

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Source of funding
	participants per group required for 80% power and SD 2.8 for a change of 2 points on the VAS scale; 71 participants in total to allow for 15% loss to follow up		Years since diagnosis	12.9 (8.9)	12.2 (8.4)				
			Type of MS: benign relapsing-remitting primary-progressive secondary progressive not known	 0 16 4 6 9	 1 12 4 13 6				
			Level of pain (baseline VAS)	7.5 (1.3)	7.9 (1.5)				
			All not significantly different.						

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding

Results:

Outcome measure Median (IQR)	Group	Week 1	Week 10	Week 16	Week 22	Percentage change from week 1 to week 10
Pain VAS	**Sham**	8 (7, 9)	4 (1, 8) p<0.0001 vs. baseline	5 (2, 7) p<0.0001 vs. baseline	5 (2, 8) p<0.0001 vs. baseline	50% improvement
	Exp.	8 (7, 9)	4 (2, 6) p<0.0001 vs. baseline; NS vs. control	5 (2, 7) p<0.0001 vs. baseline; NS vs. control	5 (1, 7) p<0.0001 vs. baseline; NS vs. control	50% improvement
McGill Pain Questionnaire Pain Rating Index (PRI 0-77)	**Sham**	24 (17, 36)	16 (6, 20) p<0.006 vs. baseline	20 (11, 27) stated to be significant vs. baseline but p not stated	22 (14, 33) NS vs. baseline	33% improvement
	Exp.	20 (16, 28)	13 (8, 21) p<0.02 vs. baseline; NS vs. control	17 (8, 30) NS vs. baseline; NS vs. control	20 (8, 30) NS vs. baseline; NS vs. control	35% improvement
McGill Pain Questionnaire Present Pain Intensity (PPI 0-5)	**Sham**	2 (1, 3)	2 (1, 2) NS vs. baseline	2 (1, 2) NS vs. baseline	2 (2, 3) NS vs. baseline	No change
	Exp.	2 (2, 3)	1 (0, 2) p<0.0001 vs. baseline; p=0.012 vs. control	2 (1, 3) NS vs. baseline; NS vs. control	2 (1, 2) stated to be significant vs. baseline and vs. control but p not stated	50% improvement
Roland Morris Disability Questionnaire	**Sham**	7 (0, 14)	1 (0, 5) p=0.002 vs. baseline	3 (0, 13) NS vs. baseline	6 (0, 15) NS vs. baseline	85% improvement
	Exp.	4 (0, 12)	0 (0, 5) p=0.03 vs. baseline; NS vs. control	2 (0, 11) NS vs. baseline; NS vs. control	0 (0, 9) NS vs. baseline; NS vs. control	100% improvement

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
Spasticity VAS	**Sham** **Exp.**	5 (1, 8) 6 (1, 8)	1 (0, 4) p<0.001 vs. baseline 1 (0, 5) p<0.003 vs. baseline; NS vs. control	3 (0, 6) NS vs. baseline 3 (0, 5) p≤0.003 vs. baseline; NS vs. control	3 (0, 5) NS vs. baseline 3 (0, 6) p≤0.003 vs. baseline; NS vs. control	80% improvement 83% improvement	
Multiple Sclerosis Impact Scale (MSIS)-29 Physical	**Sham** **Exp.**	47 (34, 64) 44 (23, 61)	31 (17, 42) p=0.002 vs. baseline 26 (12, 43) p<0.0001 vs. baseline; NS vs. control	33 (22, 61) p=0.05 vs. baseline 38 (16, 52) p=0.025 vs. baseline; NS vs. control	42 (38, 55) NS vs. baseline 39 (17, 56) NS vs. baseline; NS vs. control	34% improvement 40% improvement	
Multiple Sclerosis Impact Scale (MSIS)-29 Psychological	**Sham** **Exp.**	35 (19, 50) 36 (15, 49)	19 (6, 39) p≤0.001 vs. baseline 14 (6, 25) p≤0.001 vs. baseline; NS vs. control	24 (3, 40) p=0.012 vs. baseline 22 (8, 36) NS vs. baseline; NS vs. control	31 (14, 45) NS vs. baseline 25 (10, 44) NS vs. baseline; NS vs. control	46% improvement 61% improvement	
Modified Fatigue Impact Scale (MFIS) Physical (0-36)	**Sham** **Exp.**	24 (18, 30) 24 (16, 27)	17 (16, 22) p=0.003 vs. baseline 16 (9, 22) p<0.0001 vs. baseline; NS vs. control	20 (15, 24) NS vs. baseline 21 (12, 25) p=0.014 vs. baseline; NS vs. control	21 (18, 26) NS vs. baseline 24 (15, 30) NS vs. baseline; NS vs. control	29% improvement 33% improvement	
Modified Fatigue Impact Scale (MFIS) Cognitive (0-40)	**Sham** **Exp.**	20 (10, 24) 20 (7, 27)	14 (5, 22) p=0.023 vs. baseline 15 (3, 22) p<0.0001 vs. baseline; NS vs. control	13 (4, 18)p=0.006 vs. baseline 18 (2, 24) p=0.018 vs. baseline; NS vs. control	17 (9, 21) NS vs. baseline 17 (6, 28) NS vs. baseline; NS vs. control	30% improvement 25% improvement	
Modified Fatigue Impact	**Sham**	4 (3, 6)	3 (2, 5) p=0.023 vs. baseline	4 (1, 5) NS vs. baseline	4 (4, 6) NS vs. baseline	25% improvement	

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
Scale (MFIS) Psychological (0-40)	**Exp.**	4 (2, 6)	2 (1, 4) p=0.001 vs. baseline; NS vs. control	4 (1, 6) NS vs. baseline; NS vs. control	4 (1, 6) NS vs. baseline; NS vs. control	50% improvement	
Fatigue Severity Scale (1-7)	**Sham** **Exp.**	6 (5, 7) 5 (4, 6)	4 (4, 6) p=0.012 vs. baseline 4 (2, 5) p<0.0001 vs. baseline; NS vs. control	4 (3, 6) p=0.003 vs. baseline 5 (2, 6) NS vs. baseline; NS vs. control	5 (4, 6) NS vs. baseline 5 (3, 6) NS vs. baseline; NS vs. control	33% improvement 20% improvement	
Beck Depression Inventory (0-63)	**Sham** **Exp.**	14 (7, 18) 12 (5, 20)	10 (5, 12) p=0.004 vs. baseline 6 (3, 10) p=0.004 vs. baseline; NS vs. control	10 (2, 13) p<0.0001 vs. baseline 6 (2, 14) p=0.021 vs. baseline; NS vs. control	12 (4, 16) NS vs. baseline 9 (4, 16) NS vs. baseline; NS vs. control	29% improvement 50% improvement	
Barthel Index (0-100)	**Sham** **Exp.**	88 (75, 95) 90 (80, 95)	90 (88, 95) NS vs. baseline 95 (85, 100) NS vs. baseline; NS vs. control	86 (79, 95) NS vs. baseline 95 (85, 100) NS vs. baseline; NS vs. control	85 (75, 90) NS vs. baseline 95 (85, 100) NS vs. baseline; NS vs. control	2% improvement 5% improvement	

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Source of funding
Masoudi R, Sharifi FA, Mobasheri M, Moghadasi J. Evaluating the effectiveness of using a progressive muscle relaxation technique in reducing the pain of multiple sclerosis patients. Journal of Musculoskeletal Pain. 2013; 21(4):350-357. *(Guideline Ref ID MASOUDI2013)*	No details of randomisation, allocation concealment or blinding	N=70 N=35 in each group (No drop-outs)	Inclusion: Patients referred to a specialised referral centre. No details of pain criteria but patients scored high on VAS score at baseline Exclusion: Mental health problems, cognitive disorders			Progressive Muscle Relaxation Training Education package followed by three months practising at home	No treatment	End of treatment 3 mths	None reported
				Active N	**Control N**				
			Age 20-30 yrs 31-40 yrs	18 17	20 15				

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Source of funding
			Gender	23 females, 12 males	22 females, 13 males				
			No significant difference between groups.						
Results:									
	Group	**Before mean (SD)**		**After mean (SD)**					
Pain VAS (0-10)	**Active**	8.02 (1.70)		3.97 (1.72)					
	Control	7.94 (1.28)		8.14 (0.94)					

1

1 **Table 36: Mori 2010**

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
Mori F et al. Effects of anodal transcranial direct current stimulation on chronic neuropathic pain in patients with multiple sclerosis. J Pain 2010; 11: 436-442. MORI2010	Double-blind randomised sham-controlled trial. Computer-generated randomisation list.	19: 10 active and 9 sham treatment; none discontinued; 19 analysed	Inclusion: Relapsing-remitting MS in remitting phase; EDSS 1.5 to 6.5; with chronic drug-resistant neuropathic pain (minimum 40mm on 0-100mm pain VAS at baseline; lasting >1 month; stereotyped neurological distribution and superficial localisation; previously treated with various medications including anticonvulsants and antidepressants without satisfactory pain control). Exclusion: Patients with pain sensation corresponding to increased spastic muscle tone while passively moving the painful body segment or limb. Mean () in active treatment group and () in sham group.	Anodal transcranial direct current stimulation of the primary motor cortex contralateral to somatic painful area, 2mA for 20 minutes once a day for 5 consecutive days.	Sham transcranial direct current stimulation: electrodes placed in same position but turned off after 30 s.	Blinded assessment of outcomes at baseline, at end of 5-day treatment week, and at weeks 2, 3 and 4 (1, 2 and 3 week follow ups)	Italian National Ministerio dell'Università e della Ricerca, Italian National Ministerio della Salute, Fondazione Italiana Sclerosi Multipla (FISM); Agenzia Spaziale Italiana

	Active	Sham
Age	42.8 years	46.3 years
Gender	5 females, 5 males	6 females, 3 males

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Source of funding
			Pain duration	2.7 years	2.9 years				
			MS duration	10.1 years	10.3 years				
			EDSS	2.35	2.44				
			No significant difference between groups.						

Results (data shown graphically; some means, and SEM reported):

	Group	Week 1	Week 2	Week 3	Week 4
Pain VAS (0-100)	**Active**	45.5 (SEM 11)% of baseline value, p<0.05 vs. baseline, p<0.05 vs. sham	40.3 (SEM 10.1)% of baseline value, p<0.05 vs. baseline, p<0.05 vs. sham	40.4 (SEM 9.9)% of baseline value, p<0.05 vs. baseline, p<0.05 vs. sham	36.8 (SEM 11.2)% of baseline value p<0.05 vs. baseline, p<0.05 vs. sham
	Sham	89.3 (SEM 8.6)% of baseline value	85.2 (SEM 6.3)% of baseline value	84.7 (SEM 8.7)% of baseline value	76.3 (SEM not stated)% of baseline value
Anxiety VAS (0-100)	**Active**	NS vs. sham	NS vs. sham	NS vs. sham	NS vs. sham
	Sham				
Short Form McGill Pain Questionnaire	**Active**	p<0.05 vs. sham	p<0.05 vs. sham	p<0.05 vs. sham	p<0.05 vs. sham
	Sham				

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
Multiple Sclerosis Quality of Life-54	**Active** **Sham**	p<0.05 vs. sham	p<0.05 vs. sham	p<0.05 vs. sham		p<0.05 vs. sham	
Beck Depression Inventory	**Active** **Sham**	NS vs. sham	NS vs. sham	NS vs. sham		NS vs. sham	

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Appendix E – Forest plots

E3.1 Yoga vs control or waitlist

Figure 2: SF-36 Quality of life at 12 weeks (0-100 for each domain; higher is better outcome)

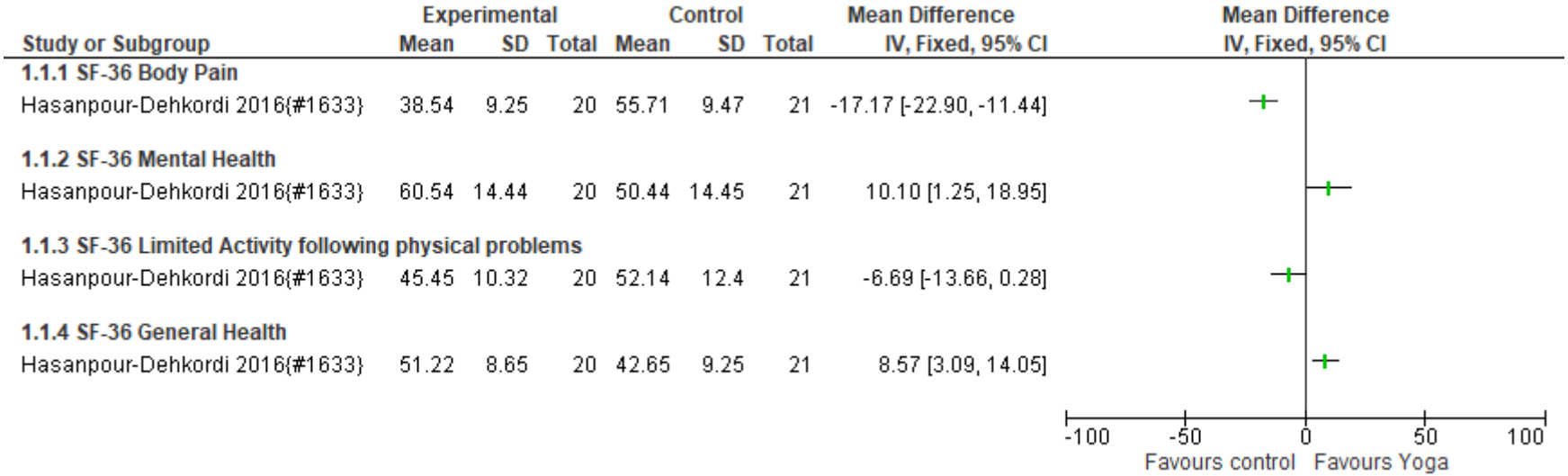

Figure 3: Pain at 1 month (MSQoL-54, 0-10 scale; higher is better outcome)

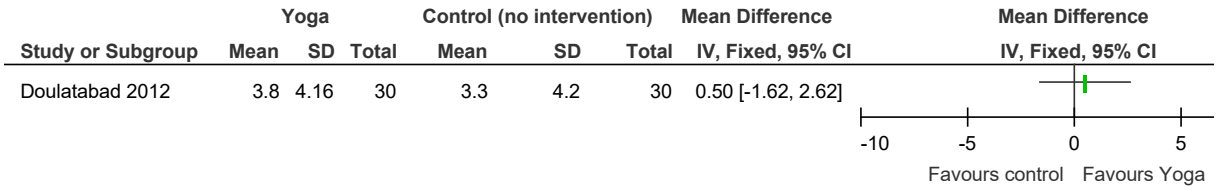

Figure 4: Quality of Life at 1 month (MSQoL-54, 0-10 scale; higher is better outcome)

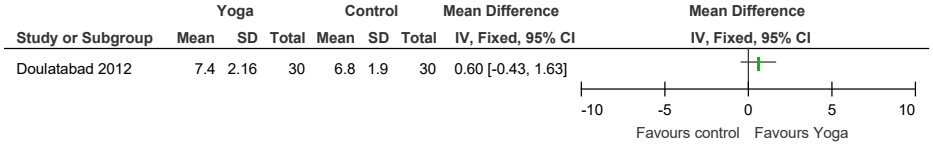

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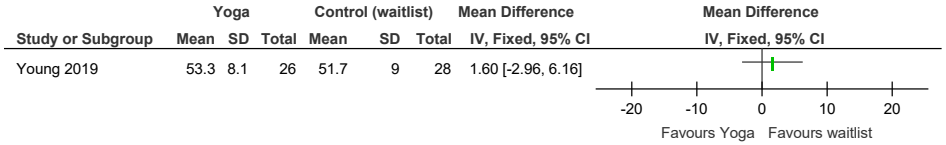
Figure 5: Pain interference at 12 weeks (PROMIS Interference short form 8a, 8-40 scale; lower is better outcome)



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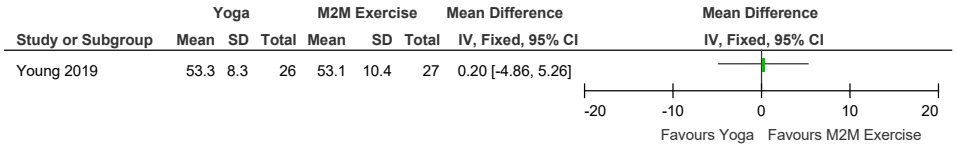
E4.2 Yoga vs Movement to Music (M2M) Exercise

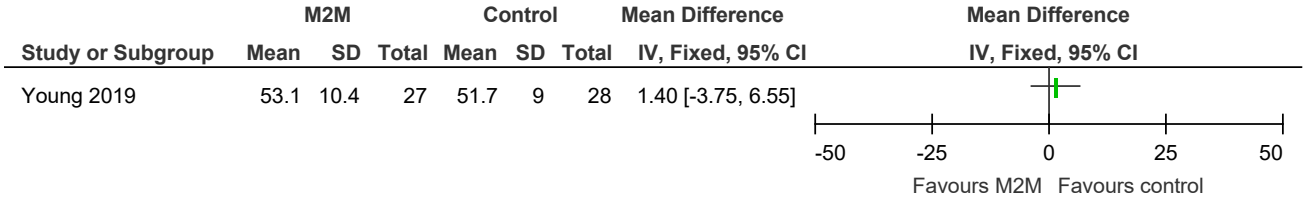
Figure 6: Pain interference at 12 weeks (PROMIS Interference short form 8a, 8-40 scale; lower is better outcome)



E13 Movement to Music (M2M) vs control

2

Figure 7: Pain interference at 12 weeks (PROMIS interference short form 8a, 8-40 scale; lower is better outcome)



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E14 Exercise (strength, stretch, endurance and balance) vs control (standard medical care, no exercise)

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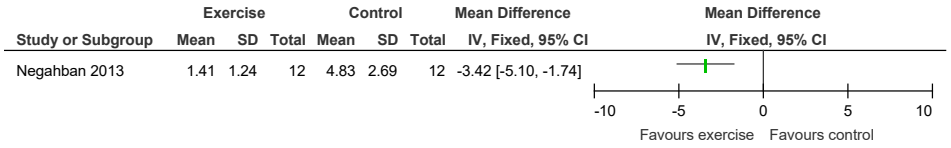
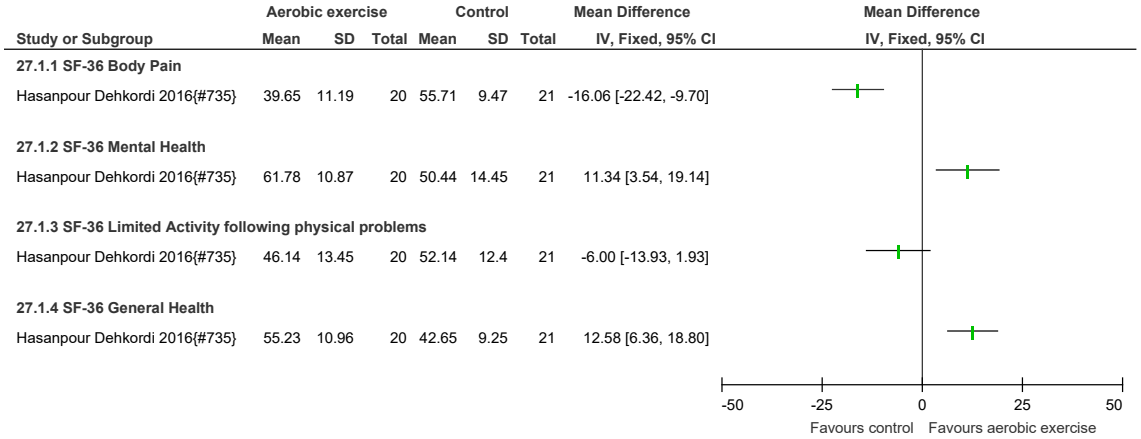
Figure 8: Pain at 5 weeks (VAS 0-10; lower is better outcome)



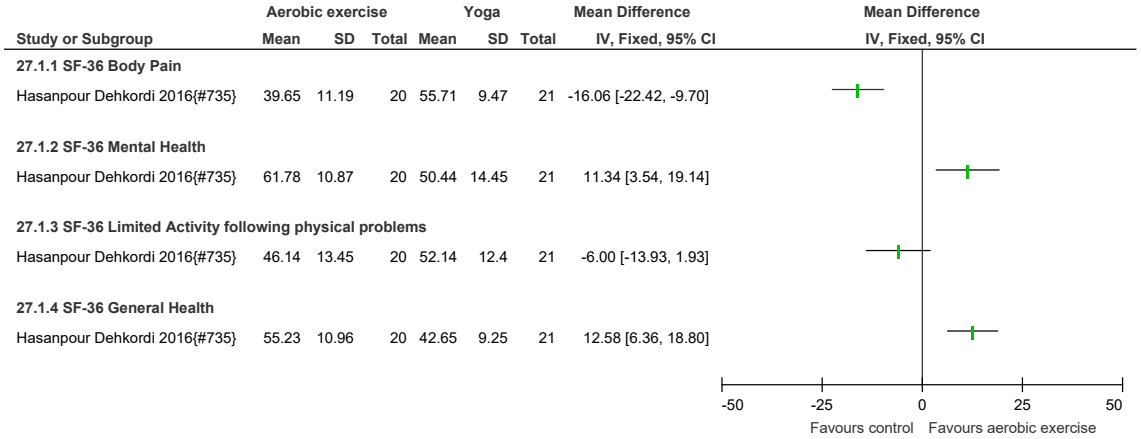
E1.5 Aerobic exercise vs control

Figure 9: SF-36 Quality of life at 12 weeks (0-100 for each domain; higher is better outcome)



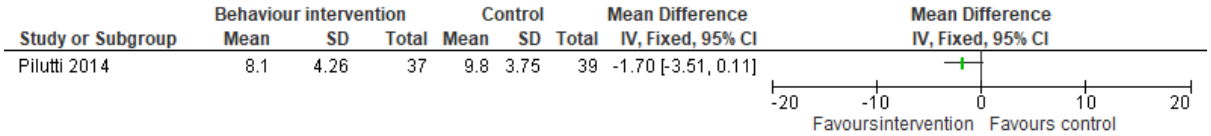
E.6 Aerobic exercise vs yoga

Figure 10: SF-36 Quality of life (0-100 for each domain; higher is better outcome)



E.7 Behavioural intervention to increase lifestyle activity vs control

Figure 11: Pain at 6 months (SF-MPQ, 0-45 scale; lower is better outcome)



Note: Baseline differences observed: Intervention 8.3 (7) and control 10.6 (7.7)

Figure 12: HADS anxiety at 6 months (0-21 scale; lower is better outcome)

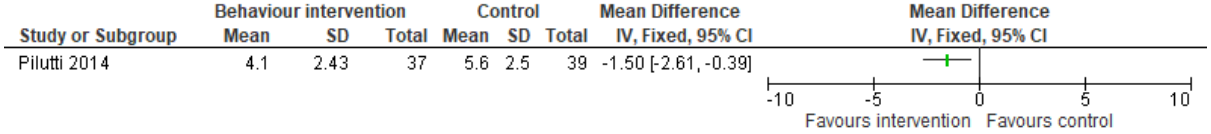


Figure 13: HADS depression at 6 months (0-21 scale; lower is better outcome)

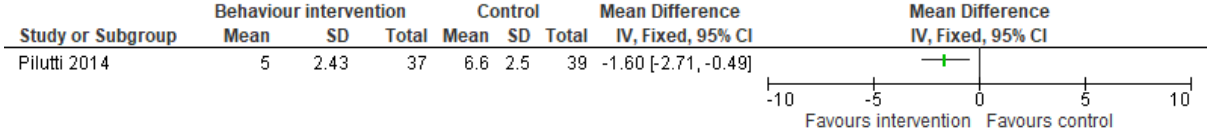
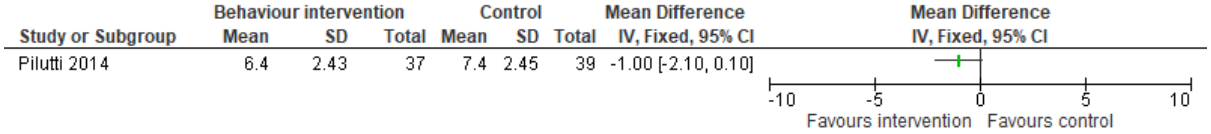
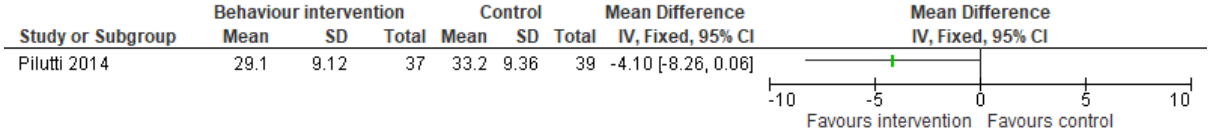


Figure 14: PSQI Global Sleep Disturbance 6 months (scale 0-21; lower is better outcome)



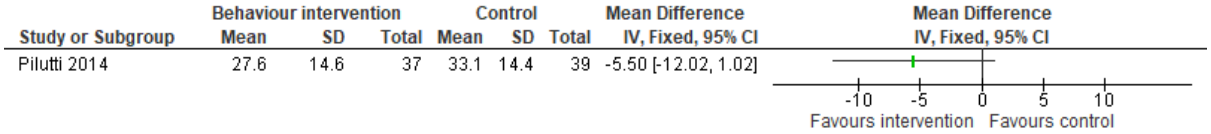
Note: Baseline differences observed: PSQI global sleep disturbance: Intervention 6.9 (4.1) and control 8.4 (4.3)

Figure 15: MSIS-29 Physical 6 months (scale 0-100; lower is better outcome)



Note: Baseline differences observed: MSIS-29 physical: intervention 28.6 (25.1) and control 34.5 (24.5)

Figure 16: MSIS 29 psychological 6 months (scale 0-100; lower is better outcome)



Note: Baseline differences observed:); MSIS 29 psychological: intervention 27.2 (21.4) and control 33.7 (23.4)

E.8 Upper limb and breathing exercise vs control

Figure 17: Pain at 4 weeks (VAS 0-5; lower is better outcome)

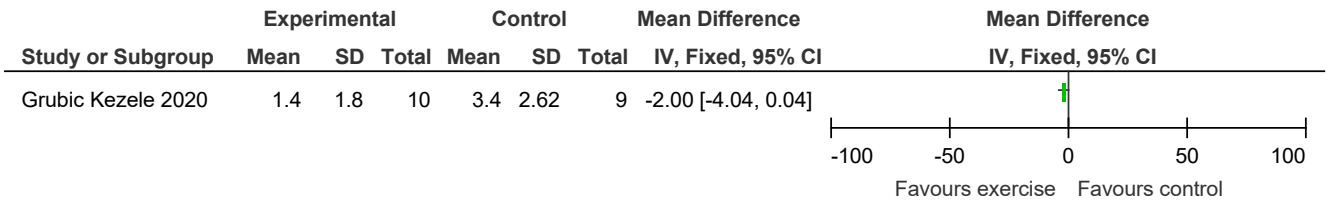


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Figure 18: Barthel Index at 4 weeks (scale 0-100; higher is better outcome)

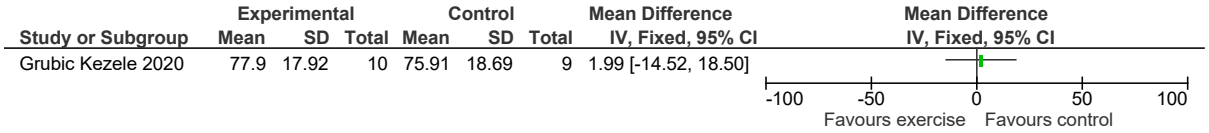

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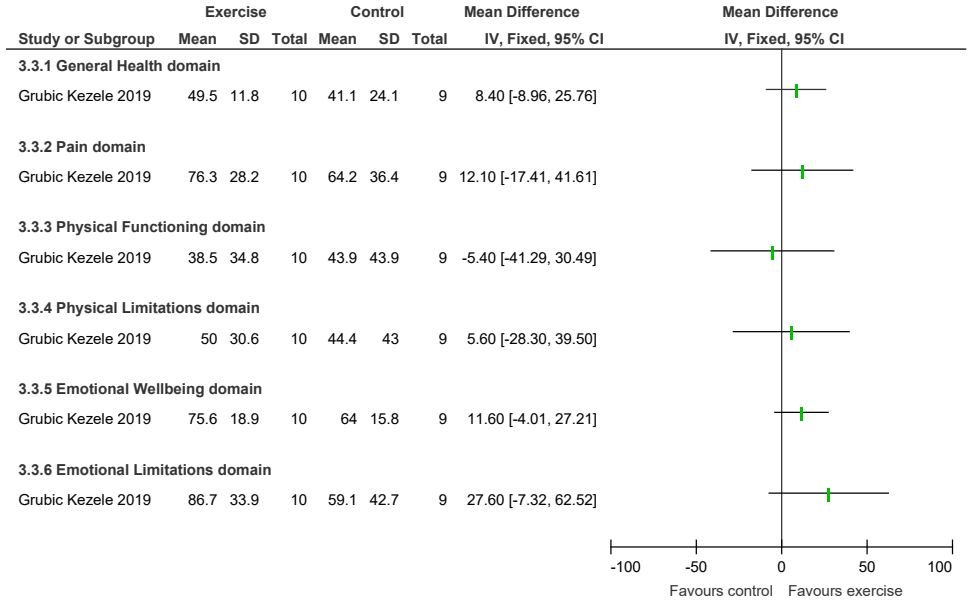
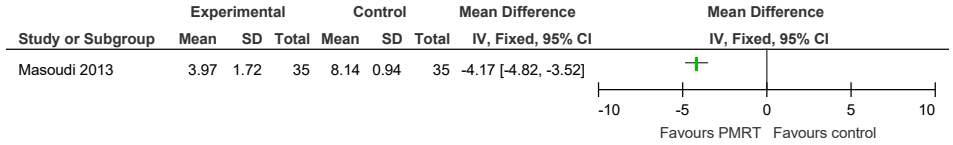
Figure 19: SF-36 Quality of life at 4 weeks (scale 0-100 for each domain; higher is better outcome)



E.9 Progressive muscle relaxation technique vs control

Figure 20: Pain at 3 months (VAS 0-10; lower is better outcome)

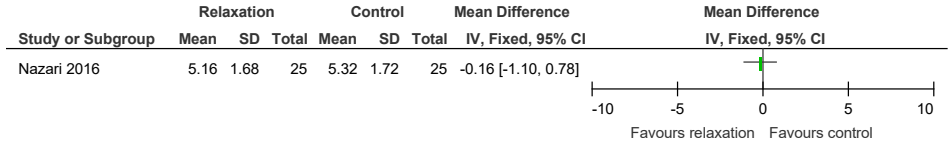


1

E.10 Relaxation vs control

3

Figure 21: Pain at 2 months (NRS, scale unclear; lower is better outcome)



4

E.11 Reflexology vs control

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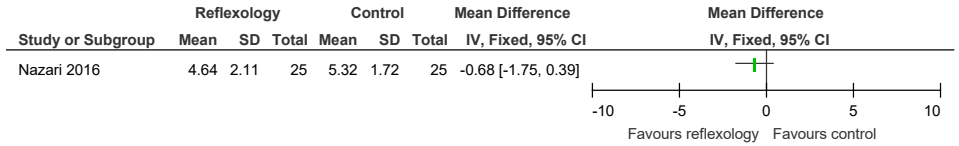
Figure 22: Pain at 2 months (NRS, scale unclear; lower is better outcome)



7

E.12 Massage vs control

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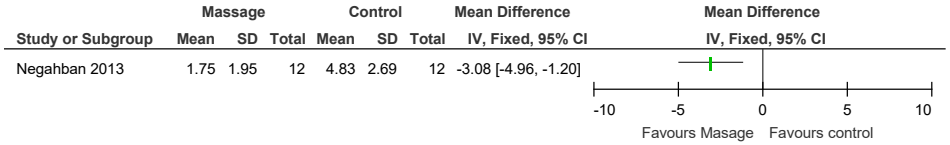
3

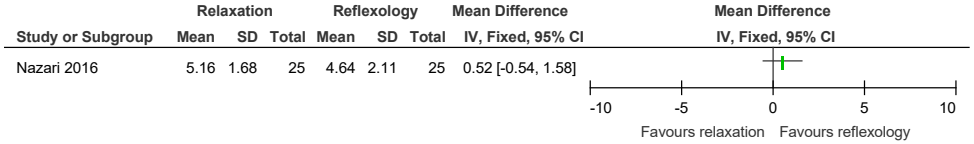
Figure 23: Pain at 5 weeks (VAS 0-10; lower is better outcome)



E.13 Relaxation vs reflexology

4
5

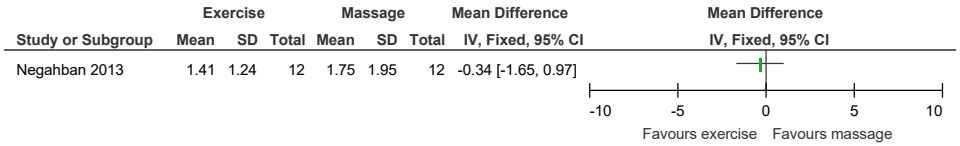
Figure 24: Pain at 2 months (NRS, scale unclear; lower is better outcome)



E.14 Exercise vs Massage

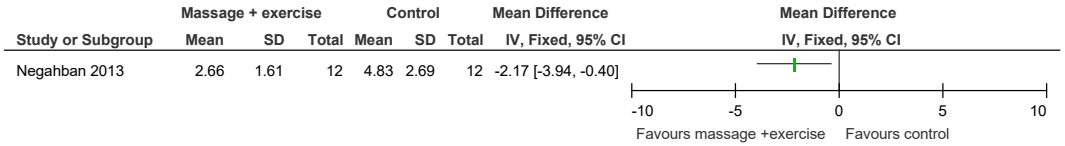
6

Figure 25: Pain at 5 weeks (VAS 0-10; lower is better outcome)



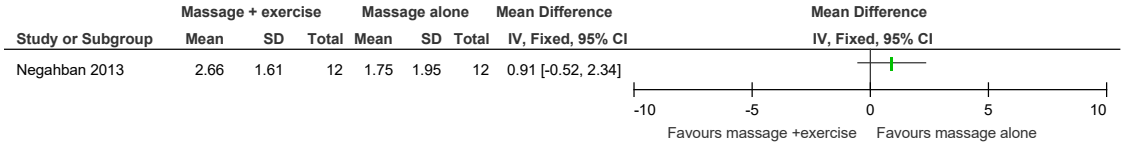
E.15 Massage + exercise vs control

Figure 26: Pain at 5 weeks (VAS 0-10; lower is better outcome)



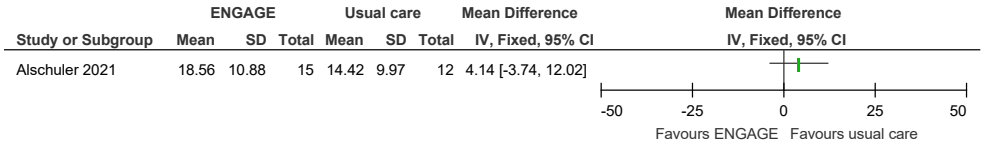
E.16 Massage + exercise vs massage alone

Figure 27: Pain at 5 weeks (VAS 0-10; lower is better outcome)



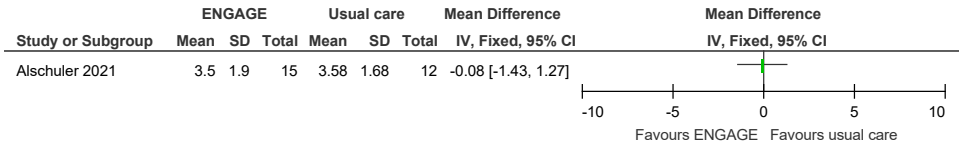
E.17 MS Education program (ENGAGE) vs Usual care

Figure 28: Pain Catastrophising at 3 months (PCS, scale 0-52; lower is better outcome



1

Figure 29: Pain intensity at 3 months (NRS, scale 0-10; lower is better outcome)



2

Figure 30: Pain interference at 3 months (PROMIS, scale unclear; lower is better outcome)

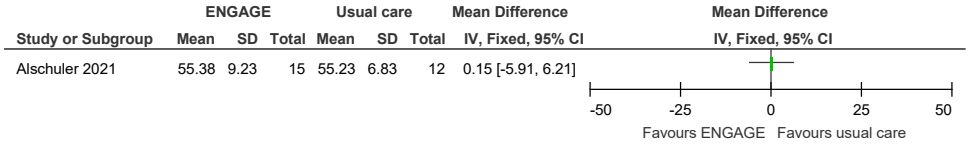
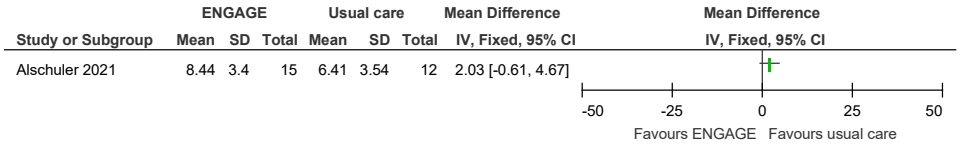


Figure 31: Depression at 3 months (PHQ-8, scale 0-24; lower is better outcome)



E.18 Self-management Programme vs control

Figure 32: Pain Interference at 6 months (BPI, scale0-10;lower is better outcome)

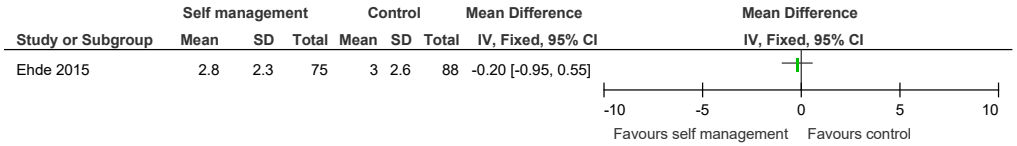
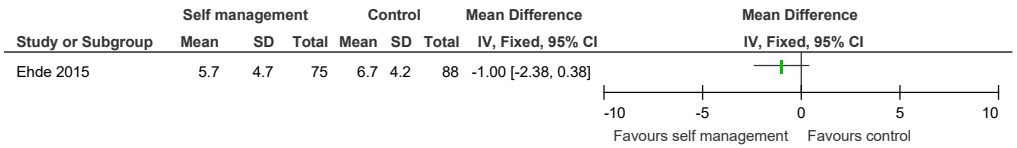
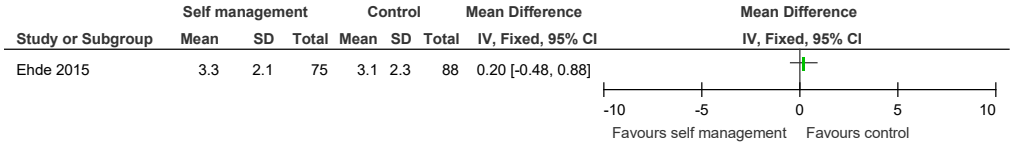


Figure 33: Depression at 6 months (PHQ-9, scale 0-27; lower is better outcome)



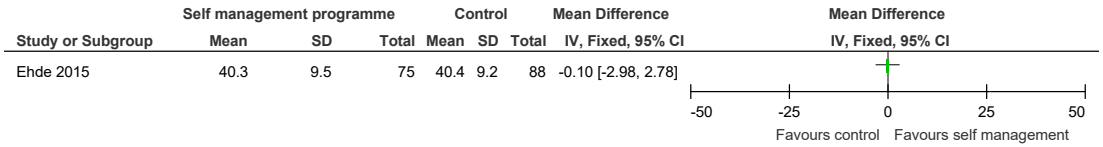
1

Figure 34: Pain intensity at 6 months (NRS, scale 0-10; lower is better outcome)



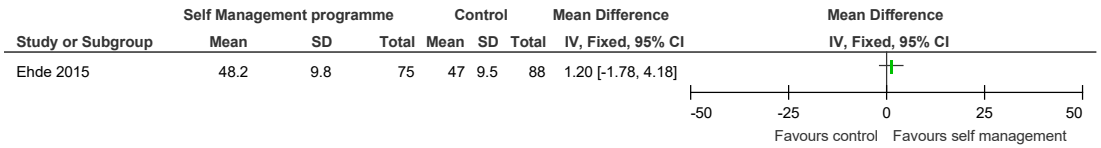
2

Figure 35: HRQoL Physical at 6 months (SF-8, scale 0-100; higher is better outcome)



3

Figure 36: HRQoL Mental at 6 months (SF-8, scale 0-100; higher is better outcome)



E.19 Hypnosis + neurofeedback vs Hypnosis alone

Figure 37: Average Pain Intensity at 1 month (NRS, scale 0-10; lower is better outcome)

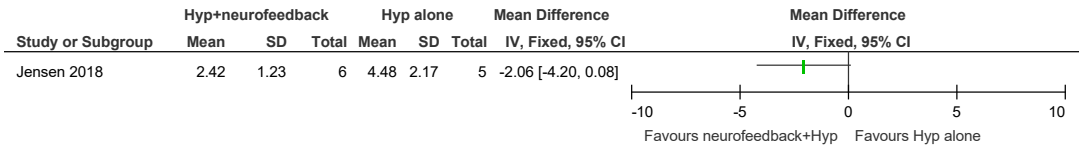


Figure 38: Pain interference at 1 month (BPI, scale likely 0-10; lower is better outcome)

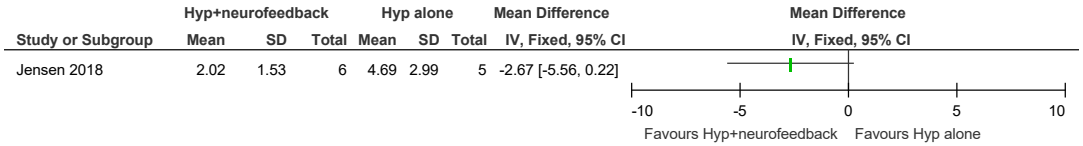


Figure 39: Pain catastrophising at 1 month (PCS, scale unclear; lower is better outcome)

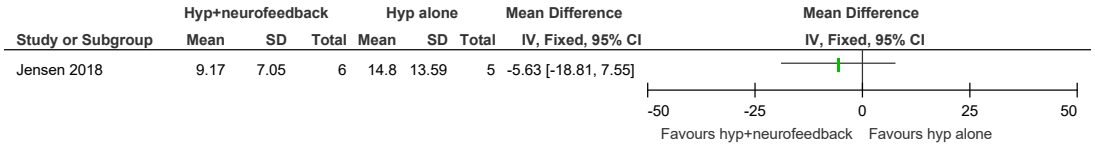


Figure 40: Pain acceptance at 1 month (CPAQ, scale unclear; lower is better outcome)

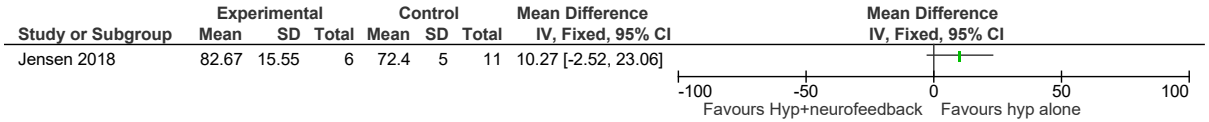
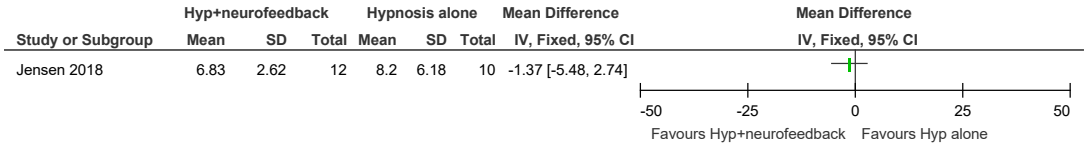
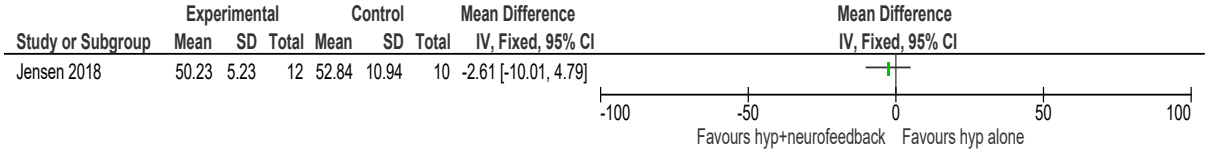


Figure 41: Depression at 1 month (PHQ-8, scale 0-24; lower is better outcome)



1

Figure 42: Sleep disturbance at 1 month (PROMIS SF-8 sleep disturbance short form 8-item version B, scale unclear; lower is better outcome)

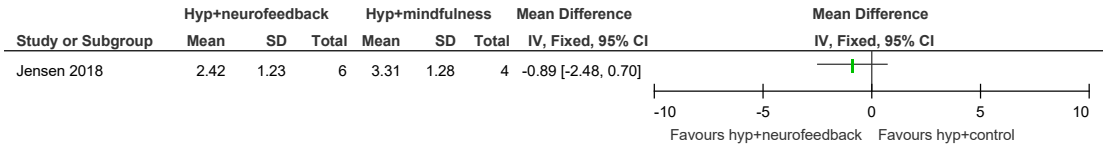


2

E.20 Hypnosis + neurofeedback vs Hypnosis +Mindfulness

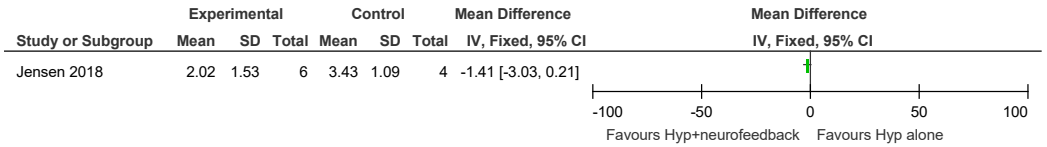
3
4

Figure 43: Average Pain Intensity at 1 month (NRS, scale0-10; lower is better outcome)



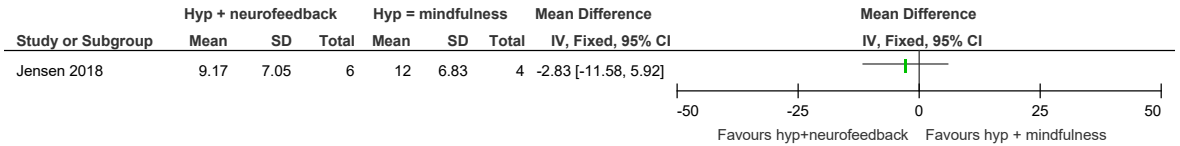
1

Figure 44: Pain interference at 1 month (BPI, scale likely 0-10; lower is better outcome)



2

Figure 45: Pain catastrophising at 1 month (PCS, scale unclear; lower is better outcome)



3

Figure 46: Pain acceptance at 1 month (CPAQ, scale unclear; lower is better outcome)

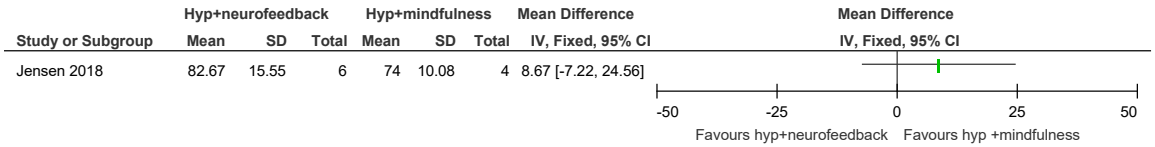


Figure 47: Depression at 1 month (PHQ-8, scale 0-24; lower is better outcome)

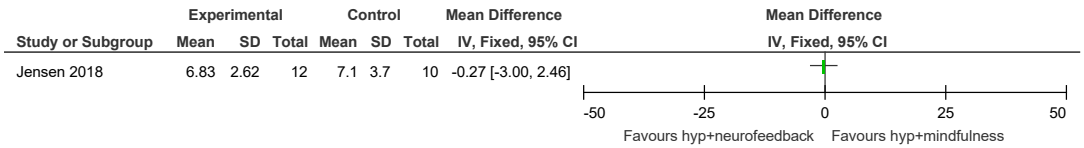
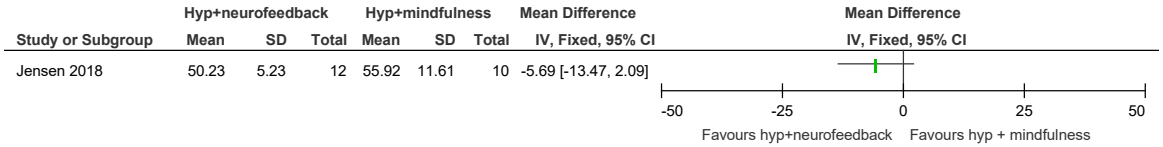


Figure 48: Sleep disturbance at 1 month (PROMIS SF-8 sleep disturbance short form 8-item version B, scale unclear; lower is better outcome)



E.21 Hypnosis +mindfulness vs Hypnosis alone

Figure 49: Average Pain Intensity at 1 month (NRS, scale0-10; lower is better outcome)

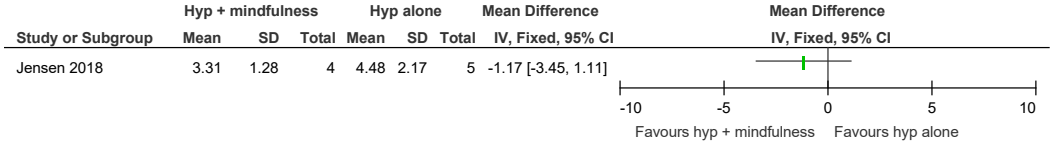


Figure 50: Pain interference at 1 month (BPI, scale likely 0-10; lower is better outcome)

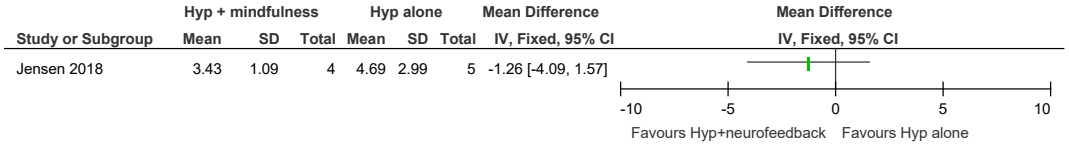
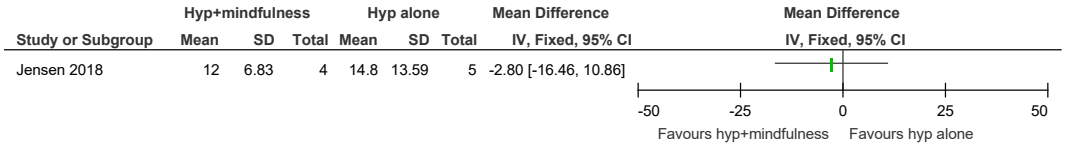
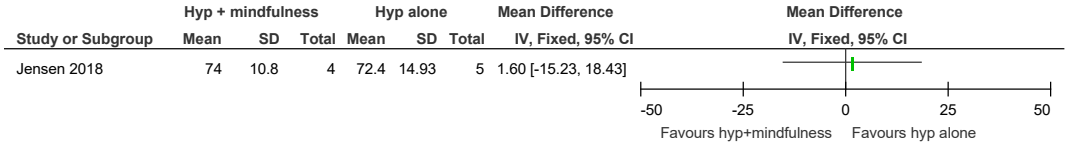


Figure 51: Pain catastrophising at 1 month (PCS, scale unclear; lower is better outcome)



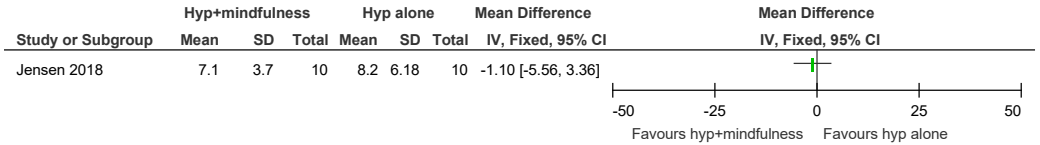
1

Figure 52: Pain acceptance at 1 month (CPAQ, scale unclear; lower is better outcome)



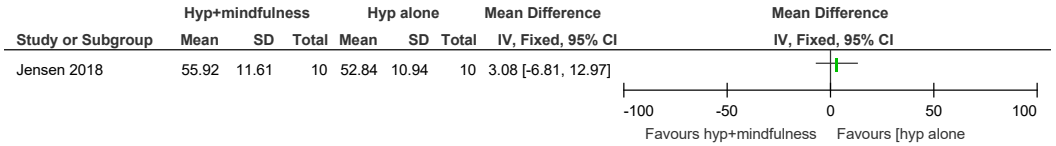
2
3

Figure 53: Depression at 1 month (PHQ-8, scale 0-24; lower is better outcome)



4

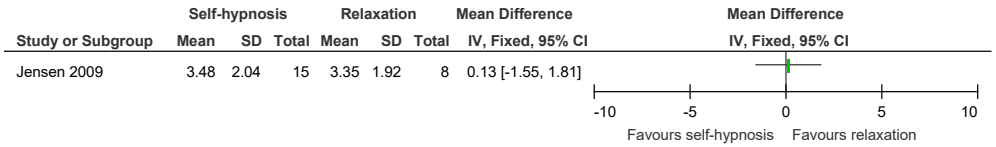
Figure 54: Sleep disturbance at 1 month (PROMIS SF-8 sleep disturbance short form 8-item version B, scale unclear; lower is better outcome)



1
2

E.22 Self-hypnosis training compared to progressive muscle relaxation

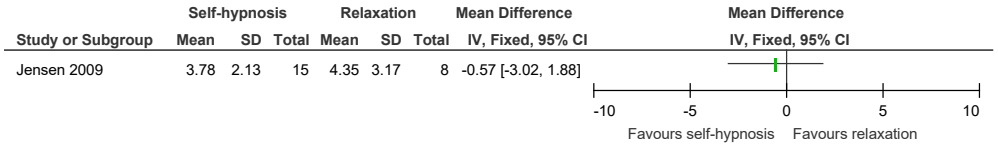
Figure 55: Pain intensity at 3 months (NRS, scale 0-10; lower is better outcome)



4

5

Figure 56: Pain interference at 3 months (modified BPI, scale likely 0-10; lower is better outcome)



E.23 Mindfulness vs control (waitlist)

Figure 57: Distress at 3 months (GHQ, scale unclear; lower is better outcome)

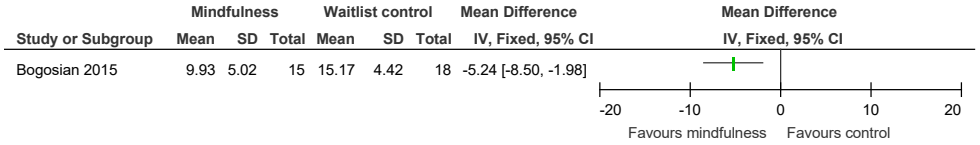
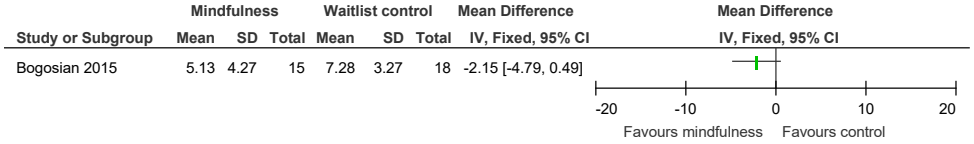
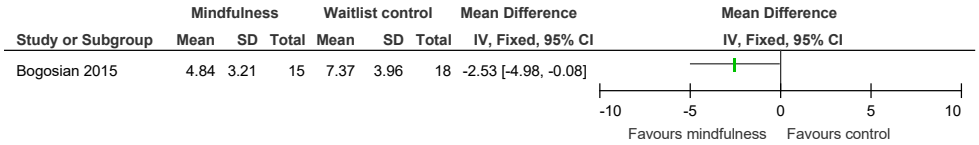


Figure 58: Depression at 3 months (HADS, scale 0-21; lower is better outcome)



1

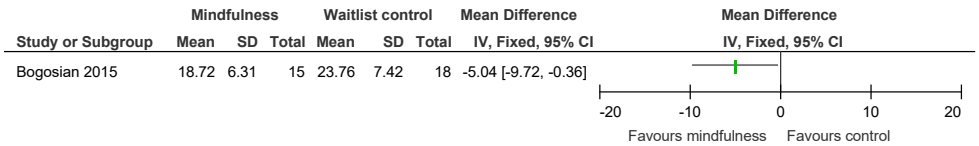
Figure 59: HADS anxiety at 3 months (scale 0-21; lower is better outcome)



2

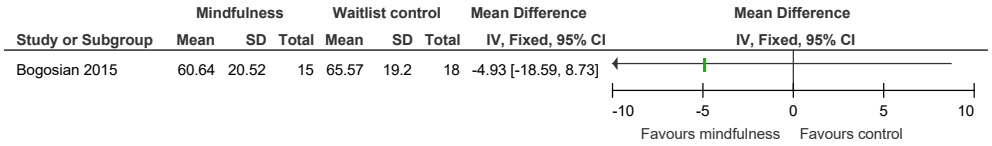
3

Figure 60: MSIS Psychological at 3 months (scale 0-100; lower is better outcome)



4

Figure 61: MSIS-physical at 3 months (scale 0-100; lower is better outcome)



5

Figure 62: Pain rating at 3 months (NRS, scale 0-10; lower is better outcome)

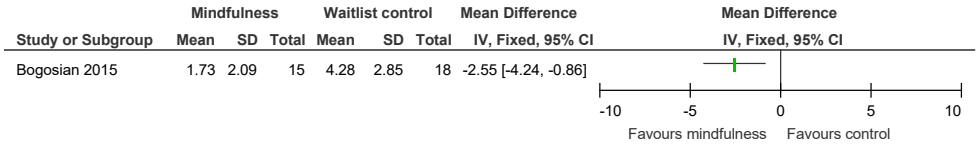
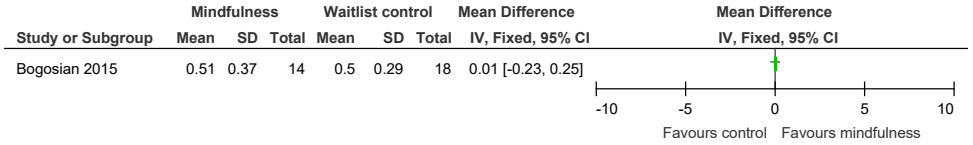
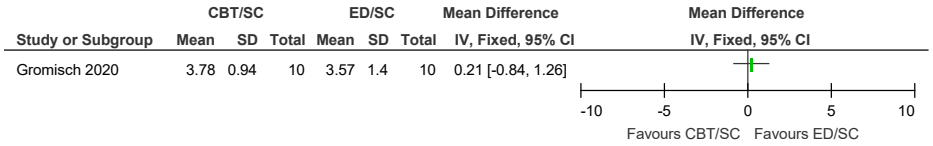


Figure 63: EQ-5D at 3 months (scale unclear; higher is better outcome)



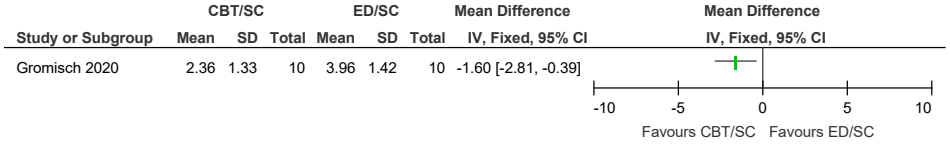
E.24 CBT + standard care (CBT/SC) vs MS education + standard care (ED/SC)

Figure 64: Pain severity at 15 weeks (scale unclear; lower is better outcome)



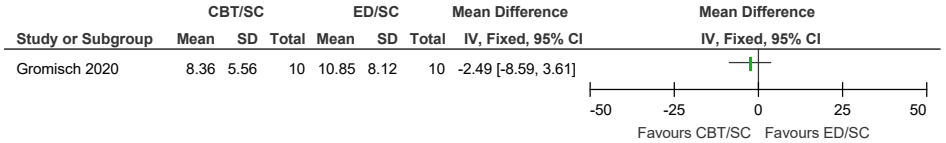
1

Figure 65: Pain interference at 15 weeks (WHYMPI interference subscale, scale unclear; lower is better outcome)



2

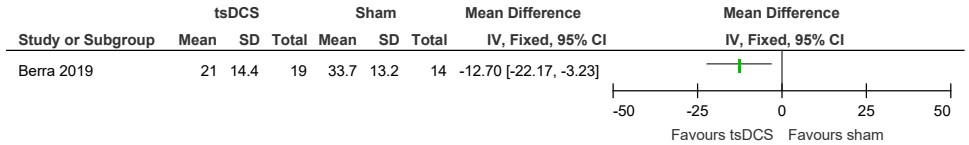
Figure 66: Depression at 15 weeks (Beck Depression Inventory, scale unclear but usually 0-63; lower is better outcome)



3

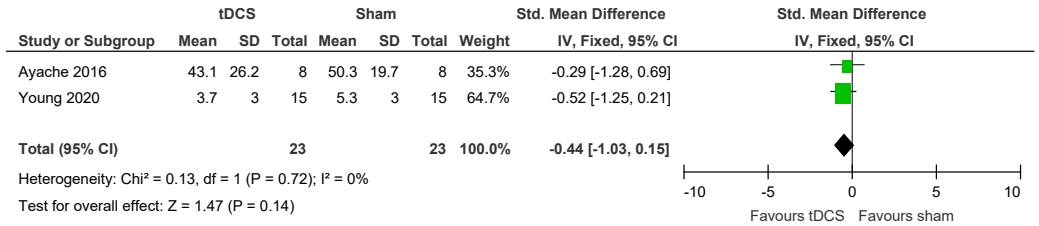
E.25 Transcutaneous Spinal Direct Current Stimulation (tsDCS) vs sham

Figure 67: Neuropathic pain symptoms inventory (NPSI) at 1 month (scale unclear; lower is better outcome)



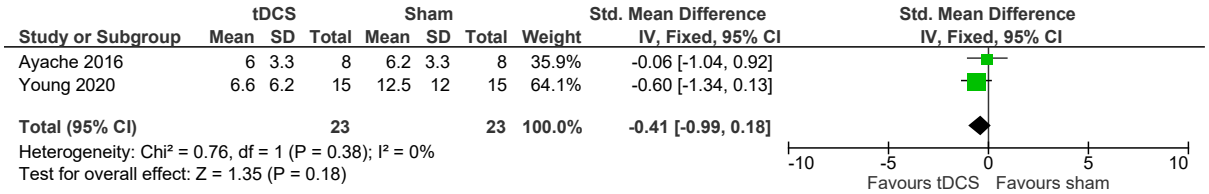
E.26 tDCS vs Sham

Figure 68: Pain at 4 weeks at 4 weeks (VAS, scale 0-100 in Ayache 2016 and unclear in Young 2020; lower is better outcome)



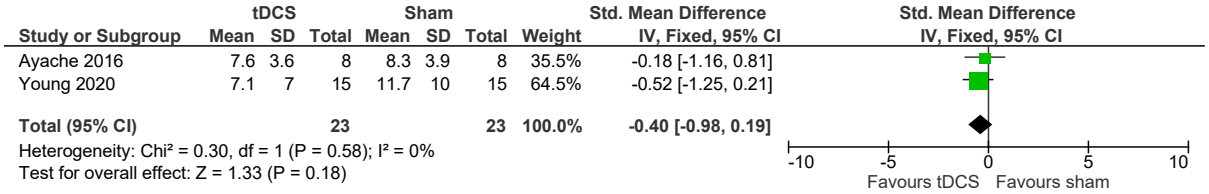
Note: this pain outcome was favoured from the Ayache 2016 study as it could be pooled with another study. Other pain outcomes reported in the Ayache 2016 study were extracted but not analysed.

Figure 69: Depression at 4 weeks (HADS or DASS, scale 0-21 for HADS in Ayache 2016 and 0-42 for DASS in Young 2020; lower is better outcome)



1

Figure 70: Anxiety at 4 weeks (HADS or DASS, scale 0-21 for HADS in Ayache 2016 and 0-42 for DASS in Young 2020; lower is better outcome)



2

Figure 71: MSQOL-54 Physical at 4 weeks (scale 0-100; higher is better outcome)

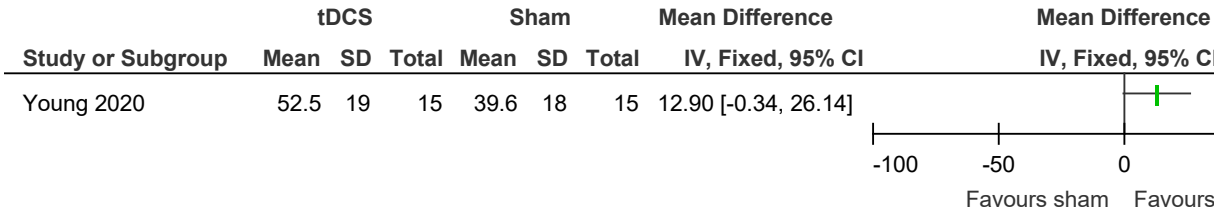


Figure 72: MSQOL-54 Mental at 4 weeks (scale 0-100; higher is better outcome)

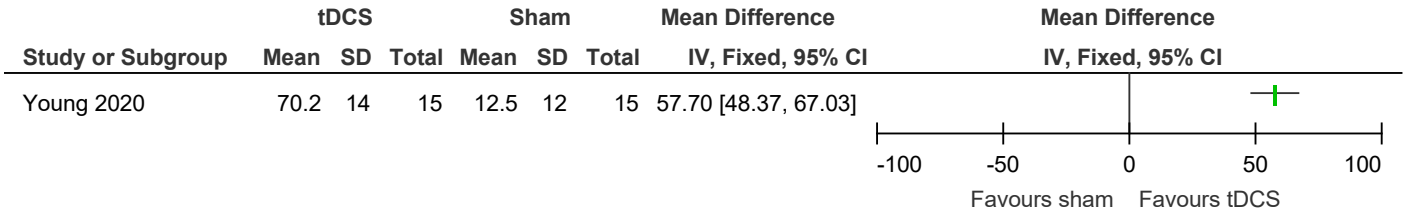
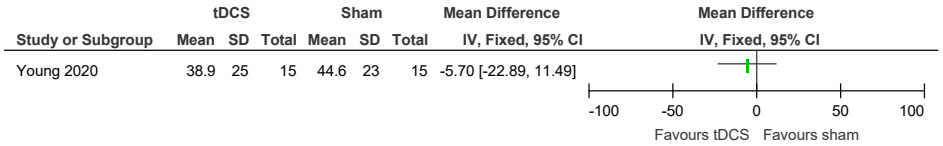
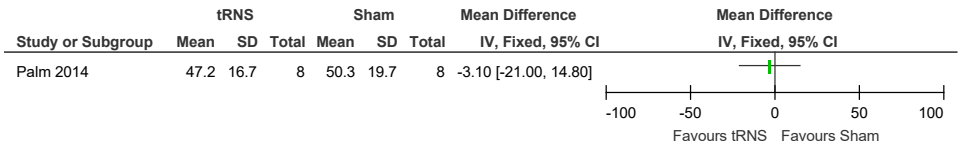


Figure 73: Neuropathic pain scale at 4 weeks (scale unclear; lower is better outcome)



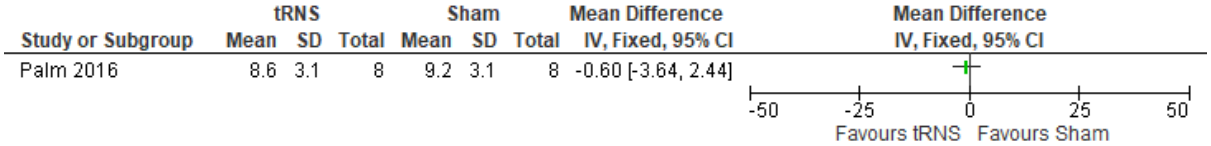
E.27 tRNS vs sham

Figure 74: VAS at 4 weeks (scale 0-100; lower is better outcome)



1

Figure 75: Brief Pain Inventory at 4 weeks (scale unclear, possibly 0-10; lower is better outcome)



2
3

Appendix F – GRADE tables

Table 37: Clinical evidence profile: Yoga versus control or waitlist

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Yoga	control or waitlist	Relative (95% CI)	Absolute (95% CI)		
SF-36 Quality of life (0-100 for each domain; higher is better outcome) - SF-36 Body Pain (follow-up: 12 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b,c]	none	20	20	-	MD **17.17 lower** (22.97 lower to 11.37 lower)	⨁◯◯◯ Very low	CRITICAL
SF-36 Quality of life (0-100 for each domain; higher is better outcome) - SF-36 Mental Health (follow-up: 12 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b,d]	none	20	20	-	MD **10.1 higher** (1.15 higher to 19.05 higher)	⨁◯◯◯ Very low	CRITICAL
SF-36 Quality of life (0-100 for each domain; higher is better outcome) - SF-36 Limited Activity following physical problems (follow-up: 12 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b,e]	none	20	20	-	MD **6.69 lower** (14.08 lower to 0.7 higher)	⨁◯◯◯ Very low	CRITICAL
SF-36 Quality of life (0-100 for each domain; higher is better outcome) - SF-36 General Health (follow-up: 12 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b,f]	none	20	20	-	MD **8.57 higher** (3.02 higher to 14.12 higher)	⨁◯◯◯ Very low	CRITICAL
Pain (MSQoL-54, 0-10 scale, higher is better outcome) (follow-up: 4 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b,g]	none	30	30	-	MD **0.5 higher** (1.62 lower to 2.62 higher)	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Yoga	control or waitlist	Relative (95% CI)	Absolute (95% CI)		
Quality of Life at 1 month (MSQoL-54, 0-10 scale, higher is better outcome) (follow-up: 4 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b,h]	none	30	30	-	MD **0.6 higher** (0.43 lower to 1.63 higher)	⨁◯◯◯ Very low	CRITICAL
Pain interference (PROMIS Interference short form 8a) (follow-up: 12 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b,i]	none	26	28	-	MD **1.6 higher** (2.96 lower to 6.16 higher)	⨁◯◯◯ Very low	CRITICAL

a. 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

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

c. MIDs used to assess imprecision were ±4.38

d. MIDs used to assess imprecision were ±7.56

e. MIDs used to assess imprecision were ±6.32

f. MIDs used to assess imprecision were ±4.75

g. MIDs used to assess imprecision were ±2.3

h. MIDs used to assess imprecision were ±0.85

i. MIDs used to assess imprecision were ±4.7

Table 38: Clinical evidence profile: Yoga versus Movement to Music (M2M) Exercise

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Yoga	M2M Exercise	Relative (95% CI)	Absolute (95% CI)		
Pain interference (PROMIS Interference short form 8a) (follow-up: 12 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b,c]	none	26	27	-	MD **0.2 higher** (4.81 lower to 5.21 higher)	⨁◯◯◯ Very low	CRITICAL

a. 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

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

c. MIDs used to assess imprecision were ±4.7

Table 39: Clinical evidence profile: M2M versus control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Movement to Music (M2M)	Control	Relative (95% CI)	Absolute (95% CI)		
Pain interference (PROMIS Interference short form 8a)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b,c]	none	27	28	-	MD **1.4 higher** (3.75 lower to 6.55 higher)	⨁◯◯◯ Very low	CRITICAL

a. 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

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

c. MIDs used to assess imprecision were ±4.9

Table 40: Clinical evidence profile: Exercise (strength, stretch, endurance and balance) versus control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Exercise (strength, stretch, endurance and balance)	control	Relative (95% CI)	Absolute (95% CI)		
Pain (VAS 0-10, Lower is better outcome) (follow-up: 5 weeks)												
1	randomised trials	serious[a]	not serious	not serious	serious[b,c]	none	12	12	-	MD **3.42 lower** (5.1 lower to 1.74 lower)	⨁⨁◯◯ Low	CRITICAL

a. 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

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

c. MIDs used to assess imprecision were ±2.02

Table 41: Clinical evidence profile: Aerobic exercise versus control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aerobic exercise	control	Relative (95% CI)	Absolute (95% CI)		
SF-36 Quality of life (0-100 for each domain; higher is better outcome) - SF-36 Body Pain (follow-up: 12 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b,c]	none	20	21	-	MD **16.06 lower** (22.42 lower to 9.7 lower)	⨁◯◯◯ Very low	CRITICAL
SF-36 Quality of life (0-100 for each domain; higher is better outcome) - SF-36 Mental Health (follow-up: 12 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b,d]	none	20	21	-	MD **11.34 higher** (3.54 higher to 19.14 higher)	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aerobic exercise	control	Relative (95% CI)	Absolute (95% CI)		
SF-36 Quality of life (0-100 for each domain; higher is better outcome) - SF-36 Limited Activity following physical problems (follow-up: 12 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b,e]	none	20	21	-	MD **6 lower** (13.93 lower to 1.93 higher)	⨁◯◯◯ Very low	CRITICAL
SF-36 Quality of life (0-100 for each domain; higher is better outcome) - SF-36 General Health (follow-up: 12 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	not serious[f]	none	20	21	-	MD **12.58 higher** (6.36 higher to 18.8 higher)	⨁⨁◯◯ Low	

a. 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

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

c. MIDs used to assess imprecision were ±4.73

d. MIDs used to assess imprecision were ±3.77

e. MIDs used to assess imprecision were ±7.07

f. MIDs used to assess imprecision were ±4.24

Table 42: Clinical evidence profile: Aerobic exercise versus yoga

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aerobic exercise	yoga	Relative (95% CI)	Absolute (95% CI)		
SF-36 Quality of life (0-100 for each domain; higher is better outcome) - SF-36 Body Pain (follow-up: 12 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aerobic exercise	yoga	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious[a]	not serious	not serious	very serious[b,c]	none	20	21	-	MD **1.11 higher** (5.19 lower to 7.41 higher)	⨁◯◯◯ Very low	CRITICAL

SF-36 Quality of life (0-100 for each domain; higher is better outcome) - SF-36 Mental Health (follow-up: 12 weeks)

1	randomised trials	very serious[a]	not serious	not serious	very serious[b,d]	none	20	21	-	MD **1.24 higher** (6.56 lower to 9.04 higher)	⨁◯◯◯ Very low	CRITICAL

SF-36 Quality of life (0-100 for each domain; higher is better outcome) - SF-36 Limited Activity following physical problems (follow-up: 12 weeks)

1	randomised trials	very serious[a]	not serious	not serious	very serious[b,e]	none	20	21	-	MD **0.69 higher** (6.67 lower to 8.05 higher)	⨁◯◯◯ Very low	CRITICAL

SF-36 Quality of life (0-100 for each domain; higher is better outcome) - SF-36 General Health (follow-up: 12 weeks)

1	randomised trials	very serious[a]	not serious	not serious	serious[b,f]	none	20	21	-	MD **4.01 higher** (2.05 lower to 10.07 higher)	⨁◯◯◯ Very low	CRITICAL

a. 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

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

c. MIDs used to assess imprecision were ±3.84

d. MIDs used to assess imprecision were ±5.55

e. MIDs used to assess imprecision were ±3.21

f. MIDs used to assess imprecision were ±5.3

1 **Table 43: Clinical evidence profile: Behavioural intervention to increase lifestyle activity versus control**

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Behavioural intervention to increase lifestyle activity	control	Relative (95% CI)	Absolute (95% CI)		
Pain[i] (SF-MPQ 0-45, lower is better outcome) (follow-up: 6 months)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b,c]	none	37	39	-	MD **1.7 lower** (3.51 lower to 0.11 higher)	⨁◯◯◯ Very low	CRITICAL
HADS anxiety (follow-up: 6 months)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b,d]	none	37	39	-	MD **1.5 lower** (2.61 lower to 0.39 lower)	⨁◯◯◯ Very low	CRITICAL
HADS depression (follow-up: 6 months)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b,e]	none	37	39	-	MD **1.6 lower** (2.71 lower to 0.49 lower)	⨁◯◯◯ Very low	CRITICAL
PSQI Global Sleep Disturbance[i] (follow-up: 6 months)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b,f]	none	37	39	-	MD **1 lower** (2.1 lower to 0.1 higher)	⨁◯◯◯ Very low	CRITICAL
MSIS-29 Physical[i] (follow-up: 6 months)												
1	randomised trials	very serious[a]	not serious	not serious	not serious[b,g]	none	37	39	-	MD **4.1 lower** (8.26 lower to 0.06 higher)	⨁⨁◯◯ Low	CRITICAL
MSIS 29 psychological[i] (follow-up: 6 months)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b,h]	none	37	39	-	MD **5.5 lower** (12.02 lower to 1.02 higher)	⨁◯◯◯ Very low	CRITICAL

a. 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

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

c. MIDs used to assess imprecision were ±3.68

d. MIDs used to assess imprecision were ±1.87

e. MIDs used to assess imprecision were ±2.02

f. MIDs used to assess imprecision were ±2.1

g. MIDs used to assess imprecision were ±12.4

h. MIDs used to assess imprecision were ±11.22

i. Baseline differences observed: Pain: Intervention 8.3 (7) and control 10.6 (7.7); PSQI global sleep disturbance: Intervention 6.9 (4.1) and control 8.4 (4.3); MSIS-29 physical: intervention 28.6 (25.1) and control 34.5 (24.5); MSIS 29 psychological: intervention 27.2 (21.4) and control 33.7 (23.4)

Table 44: Clinical evidence profile: Upper limb and breathing exercise versus control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Upper limb and breathing exercise	control	Relative (95% CI)	Absolute (95% CI)		
Pain (VAS 0-5, lower is better outcome) (follow-up: 4 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b,c]	none	10	9	-	MD **2 lower** (4.04 lower to 0.04 higher)	⊕◯◯◯ Very low	CRITICAL
Barthel Index (0-100, higher is better outcome) (follow-up: 4 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b,d]	none	10	9	-	MD **1.99 higher** (14.52 lower to 18.5 higher)	⊕◯◯◯ Very low	CRITICAL
SF-36 Quality of life (0-100 for each domain; higher is better outcome) - General Health domain (follow-up: 4 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b,e]	none	10	9	-	MD **8.4 higher** (8.96 lower to 25.76 higher)	⊕◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Upper limb and breathing exercise	control	Relative (95% CI)	Absolute (95% CI)		
SF-36 Quality of life (0-100 for each domain; higher is better outcome) - Pain domain (follow-up: 4 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b,f]	none	10	9	-	MD **12.1 higher** (17.41 lower to 41.61 higher)	⨁◯◯◯ Very low	CRITICAL
SF-36 Quality of life (0-100 for each domain; higher is better outcome) - Physical Functioning domain (follow-up: 4 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b,g]	none	10	9	-	MD **5.4 lower** (41.29 lower to 30.49 higher)	⨁◯◯◯ Very low	CRITICAL
SF-36 Quality of life (0-100 for each domain; higher is better outcome) - Physical Limitations domain (follow-up: 4 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b,h]	none	10	9	-	MD **5.6 higher** (28.3 lower to 39.5 higher)	⨁◯◯◯ Very low	CRITICAL
SF-36 Quality of life (0-100 for each domain; higher is better outcome) - Emotional Wellbeing domain (follow-up: 4 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b,i]	none	10	9	-	MD **11.6 higher** (4.01 lower to 27.21 higher)	⨁◯◯◯ Very low	CRITICAL
SF-36 Quality of life (0-100 for each domain; higher is better outcome) - Emotional Limitations domain (follow-up: 4 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b,j]	none	10	9	-	MD **27.6 higher** (7.32 lower to 62.52 higher)	⨁◯◯◯ Very low	CRITICAL

a. 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

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

c. MIDs used to assess imprecision were ±1.2

d. MIDs used to assess imprecision were ±3.47

e. MIDs used to assess imprecision were ±9.62

f. MIDs used to assess imprecision were ±18

g. MIDs used to assess imprecision were ±18.82

h. MIDs used to assess imprecision were ±17.52

i. MIDs used to assess imprecision were ±10.42

j. MIDs used to assess imprecision were ±20.47

Table 45: Clinical evidence profile: Progressive muscle relaxation technique versus control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Progressive muscle relaxation technique	control	Relative (95% CI)	Absolute (95% CI)		
Pain at 3 months (VAS 0-10; lower indicates better outcome) (follow-up: 3 months)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b,c]	none	35	35	-	MD **4.17 lower** (4.82 lower to 3.52 lower)	⨁◯◯◯ Very low	CRITICAL

a. 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

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

c. MIDs used to assess imprecision were ±0.74

Table 46: Clinical evidence profile: Relaxation versus control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relaxation	control	Relative (95% CI)	Absolute (95% CI)		
Pain (NRS, lower indicates better outcomes) (follow-up: 2 months)												
1	randomised trials	serious[a]	not serious	not serious	serious[b,c]	none	25	25	-	MD **0.16 lower** (1.1 lower to 0.78 higher)	⨁⨁◯◯ Low	CRITICAL

a. 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

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

c. MIDs used to assess imprecision were ±0.86

Table 47: Clinical evidence profile: Reflexology versus control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Reflexology	control	Relative (95% CI)	Absolute (95% CI)		
Pain (NRS, lower indicates better outcomes) (follow-up: 2 months)												
1	randomised trials	serious[a]	not serious	not serious	serious[b,c]	none	25	25	-	MD **0.68 lower** (1.75 lower to 0.39 higher)	⨁⨁◯◯ Low	CRITICAL

a. 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

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

c. MIDs used to assess imprecision were ±0.95

Table 48: Clinical evidence profile: Massage versus control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Massage	control	Relative (95% CI)	Absolute (95% CI)		
Pain at 5 weeks (VAS 0-10; lower is better outcome) (follow-up: 5 weeks)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b,c]	none	12	12	-	MD **3.08 lower** (4.96 lower to 1.2 lower)	⨁◯◯◯ Very low	CRITICAL

a. 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

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

c. MIDs used to assess imprecision were ±1.14

Table 49: Clinical evidence profile: Relaxation versus reflexology

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relaxation	reflexology	Relative (95% CI)	Absolute (95% CI)		
Pain (NRS, lower indicates better outcomes) (follow-up: 2 months)												
1	randomised trials	serious[a]	not serious	not serious	serious[b,c]	none	25	25	-	MD **0.52 higher** (0.54 lower to 1.58 higher)	⨁⨁◯◯ Low	CRITICAL

a. 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

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

c. MIDs used to assess imprecision were ±0.9

Table 50: Clinical evidence profile: Exercise versus massage

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Exercise	Massage	Relative (95% CI)	Absolute (95% CI)		
Pain (VAS 0-10; lower is better outcome) (follow-up: 5 weeks)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b,c]	none	12	12	-	MD **0.34 lower** (1.65 lower to 0.97 higher)	⨁◯◯◯ Very low	CRITICAL

a. 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

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

c. MIDs used to assess imprecision were ±0.97

Table 51: Clinical evidence profile: Massage and exercise versus control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Massage + exercise	control	Relative (95% CI)	Absolute (95% CI)		
Pain (VAS 0-10; lower is better outcome) (follow-up: 5 weeks)												
1	randomised trials	serious[a,b]	not serious	not serious	serious[b,c]	none	12	12	-	MD **2.17 lower** (3.94 lower to 0.4 lower)	⨁⨁◯◯ Low	CRITICAL

a. 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

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

c. MIDs used to assess imprecision were ±1.02

Table 52: Clinical evidence profile: Massage and exercise versus massage alone

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Massage + exercise	massage alone	Relative (95% CI)	Absolute (95% CI)		
Pain (VAS 0-10; lower is better outcome) (follow-up: 5 weeks)												
1	randomised trials	serious[a]	not serious	not serious	serious[b,c]	none	12	12	-	MD **0.91 higher** (0.52 lower to 2.34 higher)	⨁⨁◯◯ Low	CRITICAL

a. 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

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

c. MIDs used to assess imprecision were ±0.89

Table 53: Clinical evidence profile: MS education programme (ENGAGE) versus usual care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MS Education program (ENGAGE)	Usual care	Relative (95% CI)	Absolute (95% CI)		
Pain Catastrophising (PCS) (follow-up: 3 months)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b,c]	none	15	12	-	MD **4.14 higher** (3.74 lower to 12.02 higher)	⨁◯◯◯ Very low	CRITICAL
Pain intensity (NRS) (follow-up: 3 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MS Education program (ENGAGE)	Usual care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious[a]	not serious	not serious	very serious[b,d]	none	15	12	-	MD **0.08 lower** (1.43 lower to 1.27 higher)	⨁◯◯◯ Very low	CRITICAL
Pain interference (PROMIS) (follow-up: 3 months)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b,e]	none	15	12	-	MD **0.15 higher** (5.91 lower to 6.21 higher)	⨁◯◯◯ Very low	CRITICAL
Depression (PHQ-8) (follow-up: 3 months)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b,f]	none	15	12	-	MD **2.03 higher** (0.61 lower to 4.67 higher)	⨁◯◯◯ Very low	CRITICAL

a. 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

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

c. MIDs used to assess imprecision were ±4.5

d. MIDs used to assess imprecision were ±0.79

e. MIDs used to assess imprecision were ±3.11

f. MIDs used to assess imprecision were ±1.51

Table 54: Clinical evidence profile: Self-management programme versus control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Self-Management Programme	control	Relative (95% CI)	Absolute (95% CI)		
Pain intensity (NRS 0-10, lower is better outcome) (follow-up: 6 months)												
1	randomised trials	serious[a]	not serious	not serious	not serious[b]	none	75	88	-	MD **0.2 higher** (0.48 lower to 0.88 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Pain Interference (BPI 0-10, lower is better outcome) (follow-up: 6 months)												
1	randomised trials	serious[a]	not serious	not serious	not serious[c]	none	75	88	-	MD **0.2 lower** (0.95 lower to 0.55 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Depression (PHQ-9 0-27, lower is better outcome) (follow-up: 6 months)												
1	randomised trials	serious[a]	not serious	not serious	serious[d,e]	none	75	88	-	MD **1 lower** (2.38 lower to 0.38 higher)	⨁⨁◯◯ Low	CRITICAL
HRQoL Physical (SF-8) (follow-up: 6 months)												
1	randomised trials	serious[a]	not serious	not serious	not serious[f]	none	75	88	-	MD **0.1 lower** (2.98 lower to 2.78 higher)	⨁⨁⨁◯ Moderate	CRITICAL
HRQoL Mental (SF-8) (follow-up: 6 months)												
1	randomised trials	serious[a]	not serious	not serious	not serious[d,g]	none	75	88	-	MD **1.2 higher** (1.78 lower to 4.18 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Pain intensity at 12 months (NRS 0-10, lower is better outcome)												
1	randomised trials	serious[a]	not serious	not serious	not serious		75	88	-	MD **0.5 higher** (0.13 lower to 1.13 higher)	-	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Self-Management Programme	control	Relative (95% CI)	Absolute (95% CI)		
Pain Interference at 12 months (BPI 0-10, lower is better outcome)												
1	randomised trials		not serious	not serious	not serious		75	88	-	MD **0.2 higher** (0.51 lower to 0.91 higher)	-	CRITICAL
Depression at 12 months (PHQ-9 0-27, lower is better outcome)												
1	randomised trials		not serious	not serious	serious[d]		75	88	-	MD **1 lower** (2.41 lower to 0.41 higher)	-	CRITICAL
HRQoL Physical at 12 months(SF-8)												
1	randomised trials		not serious	not serious	not serious		75	88	-	MD **1.7 lower** (4.42 lower to 1.02 higher)	-	CRITICAL
HRQoL Mental at 12 months(SF-8)												
1	randomised trials		not serious	not serious	not serious		75	88	-	MD **0.5 higher** (2.45 lower to 3.45 higher)	-	CRITICAL

a. 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

b. MIDs used to assess imprecision were ±1

c. MIDs used to assess imprecision were ±102

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

e. MIDs used to assess imprecision were ±2.07

f. MIDs used to assess imprecision were ±4.02

g. MIDs used to assess imprecision were ±4.62

1

2 **Table 55: Clinical evidence profile: Hypnosis and neurofeedback versus hypnosis alone**

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hyp + neurofeedback	Hyp alone	Relative (95% CI)	Absolute (95% CI)		
Average Pain Intensity (NRS 0-10, lower is better outcome) (follow-up: 1 months)												
1	randomised trials	serious[a]	not serious	not serious	serious[b,c]	none	6	5	-	MD **2.06 lower** (4.2 lower to 0.08 higher)	⊕⊕◯◯ Low	CRITICAL
Pain interference (BPI, lower is better) (follow-up: 1 months)												
1	randomised trials	serious[a]	not serious	not serious	serious[a,d]	none	6	5	-	MD **2.67 lower** (5.56 lower to 0.22 higher)	⊕⊕◯◯ Low	CRITICAL
Pain catastrophising (PCS) (follow-up: 1 months)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b,e]	none	6	5	-	MD **5.63 lower** (18.81 lower to 7.55 higher)	⊕◯◯◯ Very low	CRITICAL
Pain acceptance (CPAQ) (follow-up: 1 months)												
1	randomised trials	serious[a]	not serious	not serious	serious[b,f]	none	12	11	-	MD **10.27 higher** (2.52 lower to 23.06 higher)	⊕⊕◯◯ Low	CRITICAL
Depression (follow-up: 1 months)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b,g]	none	12	10	-	MD **1.37 lower** (5.48 lower to 2.74 higher)	⊕◯◯◯ Very low	CRITICAL
Sleep disturbance (follow-up: 1 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hyp + neurofeedback	Hyp alone	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	very serious[b,h]	none	12	11	-	MD **2.61 lower** (10.01 lower to 4.79 higher)	⨁◯◯◯ Very low	CRITICAL

a. 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

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

c. MIDs used to assess imprecision were ±0.68

d. MIDs used to assess imprecision were ±0.69

e. MIDs used to assess imprecision were ±4.47

f. MIDs used to assess imprecision were ±9.42

g. MIDs used to assess imprecision were ±2.11

h. MIDs used to assess imprecision were ±4.21

Table 56: Clinical evidence profile: Hypnosis and neurofeedback versus hypnosis and mindfulness

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hyp + neurofeedback	Hyp +Mindfulness (at 1 month)	Relative (95% CI)	Absolute (95% CI)		
Average Pain Intensity (NRS 0-10, lower is better outcome) (follow-up: 1 months)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b,c]	none	6	4	-	MD **0.89 lower** (2.48 lower to 0.7 higher)	⨁◯◯◯ Very low	CRITICAL
Pain interference (BPI, lower is better) (follow-up: 1 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hyp + neurofeedback	Hyp +Mindfulness (at 1 month)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[b,d]	none	6	4	-	MD **1.41 lower** (3.03 lower to 0.21 higher)	⊕⊕◯◯ Low	CRITICAL
Pain catastrophising (PCS) (follow-up: 1 months)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b,e]	none	6	4	-	MD **2.83 lower** (11.58 lower to 5.92 higher)	⊕◯◯◯ Very low	CRITICAL
Pain acceptance (CPAQ) (follow-up: 1 months)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b,f]	none	6	4	-	MD **8.67 higher** (7.22 lower to 24.56 higher)	⊕◯◯◯ Very low	CRITICAL
Depression (follow-up: 1 months)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b,g]	none	12	10	-	MD **0.27 lower** (3 lower to 2.46 higher)	⊕◯◯◯ Very low	CRITICAL
Sleep disturbance (follow-up: 1 months)												
1	randomised trials	serious[a]	not serious	not serious	serious[b,h]	none	12	10	-	MD **5.69 lower** (13.47 lower to 2.09 higher)	⊕⊕◯◯ Low	CRITICAL

a. 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

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

c. MIDs used to assess imprecision were ±0.63

d. MIDs used to assess imprecision were ±0.92

e. MIDs used to assess imprecision were ±4.77

f. MIDs used to assess imprecision were ±7.14

g. MIDs used to assess imprecision were ±2.16

h. MIDs used to assess imprecision were ±4.08

Table 57: Clinical evidence profile: Hypnosis and mindfulness versus hypnosis alone

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hyp +mindfulness	Hyp alone	Relative (95% CI)	Absolute (95% CI)		
Average Pain Intensity (NRS 0-10, lower is better outcome) (follow-up: 1 months)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b,c]	none	4	5	-	MD **1.17 lower** (3.45 lower to 1.11 higher)	⨁◯◯◯ Very low	CRITICAL
Pain interference (BPI, lower is better) (follow-up: 1 months)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b,d]	none	4	5	-	MD **1.26 lower** (4.09 lower to 1.57 higher)	⨁◯◯◯ Very low	CRITICAL
Pain catastrophising (PCS) (follow-up: 1 months)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b,e]	none	4	5	-	MD **2.8 lower** (16.46 lower to 10.86 higher)	⨁◯◯◯ Very low	CRITICAL
Pain acceptance (CPAQ) (follow-up: 1 months)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b,f]	none	4	5	-	MD **1.6 higher** (15.23 lower to 18.43 higher)	⨁◯◯◯ Very low	CRITICAL
Depression (PHQ-8) (follow-up: 1 months)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b,g]	none	10	10	-	MD **1.1 lower** (5.56 lower to 3.36 higher)	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hyp +mindfulness	Hyp alone	Relative (95% CI)	Absolute (95% CI)		
Sleep disturbance (SF-8) (follow-up: 1 months)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b,h]	none	10	10	-	MD **3.08 higher** (6.81 lower to 12.97 higher)	⨁◯◯◯ Very low	CRITICAL

a. 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

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

c. MIDs used to assess imprecision were ±0.73

d. MIDs used to assess imprecision were ±1.01

e. MIDs used to assess imprecision were ±5.88

f. MIDs used to assess imprecision were ±8.63

g. MIDs used to assess imprecision were ±2.35

h. MIDs used to assess imprecision were ±4.93

Table 58: Clinical evidence profile: Self-hypnosis training versus progressive muscle relaxation

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Self-hypnosis training	progressive muscle relaxation	Relative (95% CI)	Absolute (95% CI)		
Pain intensity (NRS 0-10) (follow-up: 3 months)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b,c]	none	15	8	-	MD **0.13 higher** (1.55 lower to 1.81 higher)	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Self-hypnosis training	progressive muscle relaxation	Relative (95% CI)	Absolute (95% CI)		
Pain interference (modified BPI) (follow-up: 3 months)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b,d]	none	15	8	-	MD **0.57 lower** (3.02 lower to 1.88 higher)	⨁◯◯◯ Very low	CRITICAL

a. 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

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

c. MIDs used to assess imprecision were ±0.68

d. MIDs used to assess imprecision were ±1.28

Table 59: Clinical evidence profile: Mindfulness versus control (waitlist)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mindfulness	control (waitlist)	Relative (95% CI)	Absolute (95% CI)		
Distress (GHQ, lower is better outcome) (follow-up: 3 months)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b,c]	none	19	21	-	MD **5.24 lower** (8.18 lower to 2.3 lower)	⨁◯◯◯ Very low	CRITICAL
Depression (HADS) (follow-up: 3 months)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b,d]	none	19	21	-	MD **2.15 lower** (4.53 lower to 0.23 higher)	⨁◯◯◯ Very low	CRITICAL
HADS anxiety (follow-up: 3 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mindfulness	control (waitlist)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious[a]	not serious	not serious	serious[b,e]	none	19	21	-	MD **2.53 lower** (4.76 lower to 0.3 lower)	⨁◯◯◯ Very low	CRITICAL
MSIS Psychological (follow-up: 3 months)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b,f]	none	19	21	-	MD **5.04 lower** (9.3 lower to 0.78 lower)	⨁◯◯◯ Very low	CRITICAL
MSIS-physical (follow-up: 3 months)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b,g]	none	19	21	-	MD **4.93 lower** (17.28 lower to 7.42 higher)	⨁◯◯◯ Very low	CRITICAL
Pain rating (NRS 0-10, lower is better outcome) (follow-up: 3 months)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b,h]	none	19	21	-	MD **2.55 lower** (4.09 lower to 1.01 lower)	⨁◯◯◯ Very low	CRITICAL
EQ5D (follow-up: 3 months)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b,i]	none	19	21	-	MD **0.01 higher** (0.2 lower to 0.22 higher)	⨁◯◯◯ Very low	CRITICAL

a. 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

b. 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

c. MIDs used to assess imprecision were ±4.39

d. MIDs used to assess imprecision were ±1.71

e. MIDs used to assess imprecision were ±1.7

f. MIDs used to assess imprecision were ±2.86

g. MIDs used to assess imprecision were ±9.52

h. MIDs used to assess imprecision were ±1.41

i. MIDs used to assess imprecision were ±0.18

Table 60: Clinical evidence profile: CBT and standard care versus MS education and standard care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT + standard care(CBT/SC)	MS education + standard care (ED/SC)	Relative (95% CI)	Absolute (95% CI)		
Pain severity (follow-up: 15 weeks)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b,c]	none	10	10	-	MD **0.21 higher** (0.84 lower to 1.26 higher)	⨁◯◯◯ Very low	CRITICAL
Pain interference (WHYMPI interference subscale) (follow-up: 15 weeks)												
1	randomised trials	serious[a]	not serious	not serious	serious[b,d]	none	10	10	-	MD **1.6 lower** (2.81 lower to 0.39 lower)	⨁⨁◯◯ Low	CRITICAL
Depression (Beck Depression Inventory) (follow-up: 15 weeks)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b,e]	none	10	10	-	MD **2.49 lower** (8.59 lower to 3.61 higher)	⨁◯◯◯ Very low	CRITICAL

a. 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

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

c. MIDs used to assess imprecision were ±0.61

d. MIDs used to assess imprecision were ±0.56

e. MIDs used to assess imprecision were ±3.23

Table 61: Clinical evidence profile: Transcutaneous Spinal Direct Current Stimulation (tsDCS) versus sham

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transcutanious Spinal Direct Current Stimulation (tsDCS)	sham	Relative (95% CI)	Absolute (95% CI)		
Neuropathic pain symptoms inventory (NPSI) (follow-up: 1 months)												
1	randomised trials	serious[a]	not serious	not serious	serious[b,c]	none	19	14	-	MD **12.7 lower** (22.17 lower to 3.23 lower)	⨁⨁◯◯ Low	CRITICAL

a. 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

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

c. MIDs used to assess imprecision were ±9.82

Table 62: Clinical evidence profile: Transcutaneous Direct Current Stimulation (tDCS) versus sham

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	tDCS	Sham	Relative (95% CI)	Absolute (95% CI)		
Pain (VAS) (follow-up: 4 weeks)												
2	randomised trials	serious[a]	not serious	not serious	not serious[b]	none	23	23	-	SMD **0.44 lower** (1.03 lower to 0.15 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Depression (DASS or HADS) (follow-up: 4 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	tDCS	Sham	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	very serious[a]	not serious	not serious	not serious[c]	none	23	23	-	SMD **0.41 SD lower** (0.99 lower to 0.18 higher)	⨁⨁◯◯ Low	CRITICAL
Anxiety (DASS or HADS) (follow-up: 4 weeks)												
2	randomised trials	very serious[a]	not serious	not serious	not serious[d]	none	23	23	-	SMD **0.4 SD lower** (0.98 lower to 0.19 higher)	⨁⨁◯◯ Low	CRITICAL
MSQOL-54 Physical (follow-up: 4 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	serious[e,f]	none	15	15	-	MD **12.9 higher** (0.34 lower to 26.14 higher)	⨁◯◯◯ Very low	CRITICAL
MSQOL-54 Mental (follow-up: 4 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	not serious[g]	none	15	15	-	MD **57.7 higher** (48.37 higher to 67.03 higher)	⨁⨁◯◯ Low	CRITICAL
Pain (NPS) (follow-up: 4 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[h]	none	15	15	-	MD **5.7 lower** (22.89 lower to 11.49 higher)	⨁◯◯◯ Very low	CRITICAL

a. 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

b. MIDs used to assess imprecision were ±5.3

c. MIDs used to assess imprecision were ±2.7

d. MIDs used to assess imprecision were ±2.6

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

f. MIDs used to assess imprecision were ±9.25

g. MIDs used to assess imprecision were ±9.75

h. MIDs used to assess imprecision were ±8.25

Table 63: Clinical evidence profile: Transcutaneous Random Noise Stimulation (tRNS) versus sham

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	tRNS	sham	Relative (95% CI)	Absolute (95% CI)		
VAS (0-100) (follow-up: 4 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b,c]	none	8	8	-	MD **3.1 lower** (21 lower to 14.8 higher)	⨁◯◯◯ Very low	CRITICAL
Brief Pain Inventory (Global score) (follow-up: 4 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[d]	none	8	8	-	MD **0.6 lower** (3.64 lower to 2.44 higher)	⨁◯◯◯ Very low	CRITICAL

a. 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

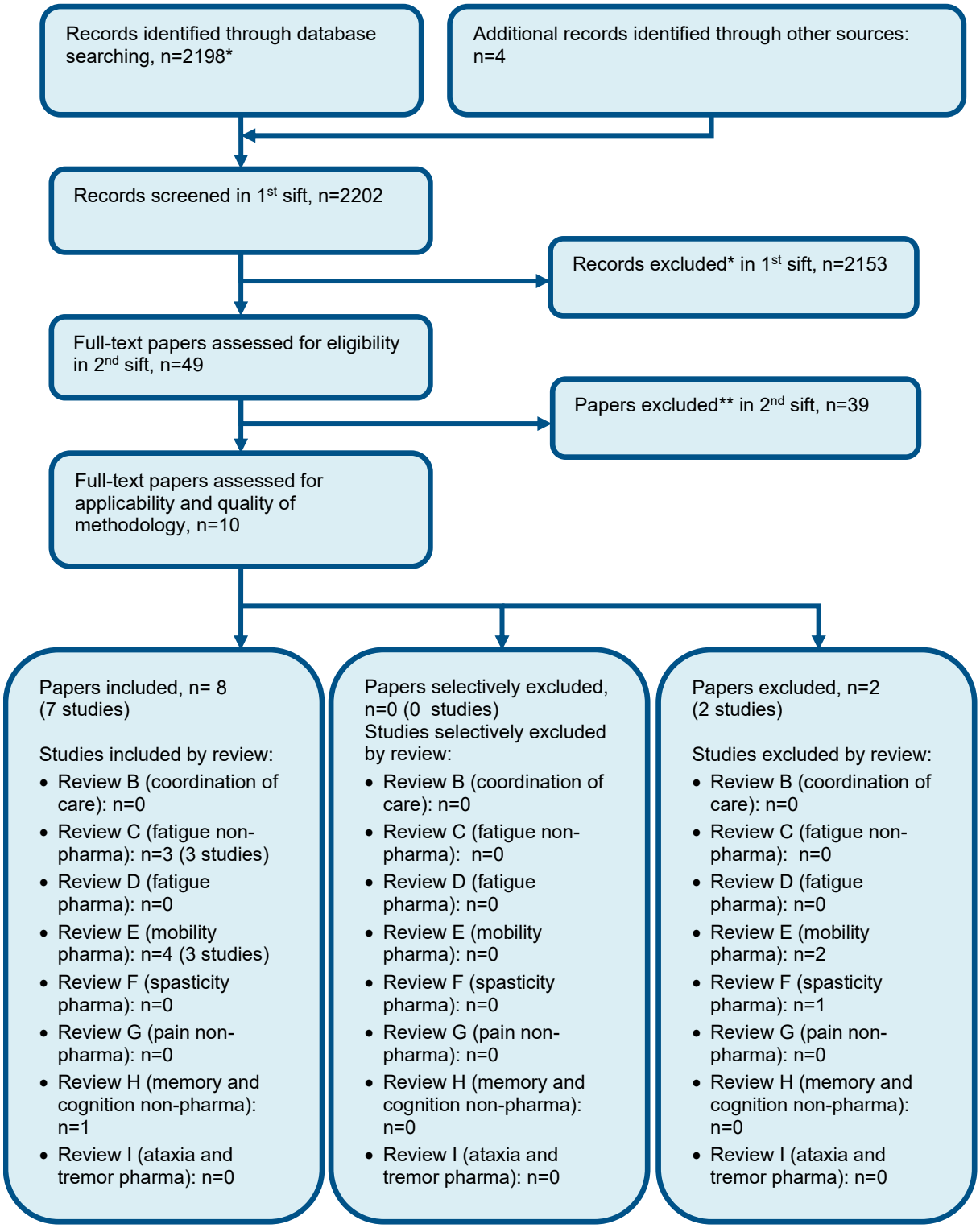
b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. MIDs used to assess imprecision were ±10.52

d. MIDs used to assess imprecision were ±1.47

Appendix G Economic evidence study selection

Figure 76: Flow chart of health economic study selection for the guideline



* Excluding conference abstracts.
**Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H – Economic evidence tables

None.

Appendix I – Health economic model

No original economic modelling was undertaken.

1

1 Appendix J – Excluded studies

2 Clinical studies

3 Table 64: Studies excluded from the clinical review

Study	Code [Reason]
Aguera, E., Caballero-Villarraso, J., Feijoo, M. et al. (2020) Clinical and neurochemical effects of transcranial magnetic stimulation (TMS) in multiple sclerosis: A study protocol for a randomized clinical trial. Frontiers in Neurology. 11: 750	- study protocol
Amatya, B.; Young, J.; Khan, F. (2018) Non-pharmacological interventions for chronic pain in multiple sclerosis. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies
Bikmoradi, A., Zafari, A., Oshvandi, K. et al. (2014) Effect of progressive muscle relaxation on severity of pain in patients with multiple sclerosis: a randomized controlled trial. HAYAT 20(1): 26-37	- Study not reported in English
Castelnuovo, G., Giusti, E. M., Manzoni, G. M. et al. (2016) Psychological treatments and psychotherapies in the neurorehabilitation of pain: evidences and recommendations from the Italian Consensus Conference on Pain in Neurorehabilitation. Frontiers in Psychology 7: 115	- Systematic review used as source of primary studies
Connolly, G. W. (2013) Pain in multiple sclerosis. Dissertation/ thesis	- Time-point short compared to other included studies (only 2 weeks)- Not a peer-reviewed publication
Daniali, S. S., Shahnazi, H., Kazemi, S. et al. (2016) The effect of educational intervention on knowledge and self-efficacy for pain control in patients with multiple sclerosis. Materia Sociomedica 28(4): 283-287	- No outcomes of interest
David, Mcmm, Moraes, A. A., Costa, M. L. D. et al. (2018) Transcranial direct current stimulation in the modulation of neuropathic pain: a systematic review. Neurological Research 40(7): 555-563	- Systematic review used as source of primary studies
Demaneuf, T., Aitken, Z., Karahalios, A. et al. (2019) Effectiveness of exercise interventions	- Systematic review used as source of primary studies

Study	Code [Reason]
for pain reduction in people with multiple sclerosis: A systematic review and meta-analysis of randomized controlled trials. Archives of Physical Medicine & Rehabilitation 100(1): 128-139	
Di Stefano, G.; Maarbjerg, S.; Truini, A. (2019) Trigeminal neuralgia secondary to multiple sclerosis: from the clinical picture to the treatment options. Journal of Headache & Pain 20(1): 20	- Study does not contain an intervention relevant to this review protocol
Ehde, D. M., Alschuler, K. N., Day, M. A. et al. (2019) Mindfulness-based cognitive therapy and cognitive behavioural therapy for chronic pain in multiple sclerosis: a randomized controlled trial protocol. Trials 20(1): 774	- study protocol
Ehde, D. M., Alschuler, K. N., Sullivan, M. D. et al. (2018) Improving the quality of depression and pain care in multiple sclerosis using collaborative care: The MS-care trial protocol. Contemporary Clinical Trials 64: 219-229	- study protocol
Ehde, D. M., Arewasikporn, A., Alschuler, K. N. et al. (2018) Moderators of treatment outcomes after telehealth self-management and education in adults with multiple sclerosis: A secondary analysis of a randomized controlled trial. Archives of Physical Medicine & Rehabilitation 99(7): 1265-1272	- Data not reported in an extractable format or a format that can be analysed *Secondary analysis providing correlation coefficients No efficacy data*
Gholami, M., Nami, M., Shamsi, F. et al. (2021) Effects of transcranial direct current stimulation on cognitive dysfunction in multiple sclerosis. Neurophysiologie Clinique 01: 01	- No outcomes of interest
Han, A. (2021) Mindfulness-and acceptance-based interventions for symptom reduction of people with multiple sclerosis: A systematic review and meta-analysis. Archives of Physical Medicine & Rehabilitation 102(10): 2022-2031.e4	- Systematic review used as source of primary studies
Hochsprung, A., Escudero-Uribe, S., Ibanez-Vera, A. J. et al. (2021) Effectiveness of monopolar dielectric transmission of pulsed electromagnetic fields for multiple sclerosis-related pain: A pilot study. Neurologia 36(6): 433-439	- Study not reported in English

Study	Code [Reason]
Hosseinzadegan, F., Radfar, M., Shafiee, A. et al. (2015) The effect of self-hypnosis on severity and quality of pain in women with multiple sclerosis: A Randomized clinical trial. Journal of Nursing & Midwifery 13(4): 292-300	- Study not reported in English
Hosseinzadegan, F., Radfar, M., Shafiee-Kandjani, A. R. et al. (2017) Efficacy of self-hypnosis in pain management in female patients with multiple sclerosis. International Journal of Clinical & Experimental Hypnosis 65(1): 86-97	- Data not reported in an extractable format or a format that can be analysed
Hsu, W. Y., Cheng, C. H., Zanto, T. P. et al. (2021) Effects of transcranial direct current stimulation on cognition, mood, pain, and fatigue in multiple sclerosis: A systematic review and meta-analysis. Frontiers in Neurology. 12: 626113	- Systematic review used as source of primary studies
Ibarra, A. M. C., Biasotto-Gonzalez, D. A., Kohatsu, E. Y. I. et al. (2021) Photobiomodulation on trigeminal neuralgia: systematic review. Lasers in Medical Science 36, 715–722	- Systematic review used as source of primary studies
Ibrahim, F. A., Al Sebaee, H. A., El Deen, D. S. et al. (2020) Effect of acupressure pain and fatigue among patients with multiple sclerosis. Indian Journal of Public Health Research and Development 11(3): 1973-1978	- Population not relevant to this review protocol
Jawahar, R., Oh, U., Yang, S. et al. (2014) Alternative approach: a systematic review of non-pharmacological non-spastic and non-trigeminal pain management in multiple sclerosis. European journal of physical & rehabilitation medicine. 50(5): 567-77	- Systematic review used as source of primary studies *Identified in surveillance review. All studies checked and were either included in previous guideline or do not fit the protocol.*
Karpatkin, H. I.; Napolione, D.; Siminovich-Blok, B. (2014) Acupuncture and multiple sclerosis: a review of the evidence. Evidence-Based Complementary & Alternative Medicine. 2014: 972935	- Systematic review used as source of primary studies
Kiropoulos, L. A., Kilpatrick, T., Holmes, A. et al. (2016) A pilot randomized controlled trial of a tailored cognitive behavioural therapy-based intervention for depressive symptoms in those newly diagnosed with multiple sclerosis. BMC Psychiatry 16(1): 435	- No outcomes of interest *Primary outcomes for depression related. Pain impact was a secondary outcome but only in terms of its effect on mood. "The Pain Effects Scale (PES) [31] was used to measure the level of impact that pain had on mood and behaviour.*

Study	Code [Reason]
	Higher scores indicate a greater impact of pain on a patient's mood and behaviour"
Kiropoulos, L., Kilpatrick, T., Kalincik, T. et al. (2020) Comparison of the effectiveness of a tailored cognitive behavioural therapy with a supportive listening intervention for depression in those newly diagnosed with multiple sclerosis (the ACTION-MS trial): protocol of an assessor-blinded, active comparator, randomised controlled trial. Trials 21(1): 100	- study protocol *Trial still ongoing*
Knowles, L. M., Arewasikporn, A., Kratz, A. L. et al. (2020) Early treatment improvements in depression are associated with overall improvements in fatigue impact and pain interference in adults with multiple sclerosis. Annals of Behavioral Medicine 16: 16	- Data not reported in an extractable format or a format that can be analysed *Secondary analysis looking at whether treatment improving one symptom is associated with improvement in others.*
Kubsik, A., Klimkiewicz, R., Klimkiewicz, P. et al. (2016) Assessment of the pain patients with the multiple sclerosis after applying the physiotherapy treatment. Polski Merkuriusz Lekarski 40(238): 230-234	- Study not reported in English
Minen, M. T.; Schaubhut, K. B.; Morio, K. (2020) Smartphone based behavioural therapy for pain in multiple sclerosis (MS) patients: A feasibility acceptability randomized controlled study for the treatment of comorbid migraine and MS pain. Multiple Sclerosis and Related Disorders 46: 102489	- Study does not contain an intervention relevant to this review protocol *The study assess the use of a smartphone app in delivering progressive muscle training (PMR) rather than the effectiveness of PMR itself.*
Mooventhan, A. and Nivethitha, L. (2017) Evidence based effects of yoga in neurological disorders. Journal of Clinical Neuroscience 43: 61-67	- Systematic review used as source of primary studies
Muller, R., Gertz, K. J., Molton, I. R. et al. (2016) Effects of a tailored positive psychology intervention on well-being and pain in individuals with chronic pain and a physical disability: A feasibility trial. Clinical Journal of Pain 32(1): 32-44	- Mixed population (<60% MS patients) *Mixed population, % of MS not clear. Other evidence available so can exclude as per protocol criteria*
Palm, U., Ayache, S. S., Padberg, F. et al. (2014) Non-invasive brain stimulation therapy in multiple sclerosis: a review of tDCS, rTMS and ECT results. Brain Stimulation 7(6): 849-54	- Systematic review used as source of primary studies
Pilutti, L. A., Edwards, T., Motl, R. W. et al. (2019) Functional electrical stimulation cycling	- Study does not contain an intervention relevant to this review protocol

Study	Code [Reason]
exercise in people with multiple sclerosis: secondary effects on cognition, symptoms, and quality of life. International Journal of MS Care 21(6): 258-264	
Rimmer, J. H., Thirumalai, M., Young, H. J. et al. (2018) Rationale and design of the tele-exercise and multiple sclerosis (TEAMS) study: A comparative effectiveness trial between a clinic- and home-based telerehabilitation intervention for adults with multiple sclerosis (MS) living in the deep south. Contemporary Clinical Trials 71: 186-193	- study protocol *Still recruiting*
Salarvand, S., Heidari, M. E., Farahi, K. et al. (2021) Effectiveness of massage therapy on fatigue and pain in patients with multiple sclerosis: A systematic review and meta-analysis. Multiple Sclerosis Journal Experimental Translational & Clinical 7(2): 20552173211022779	- Systematic review used as source of primary studies
Sawant, A., Dadurka, K., Overend, T. et al. (2015) Systematic review of efficacy of TENS for management of central pain in people with multiple sclerosis. Multiple Sclerosis and Related Disorders 4(3): 219-27	- Systematic review used as source of primary studies *Identified in surveillance review. All studies checked and were either included in previous guideline or do not fit the protocol.*
Senders, A., Hanes, D., Bourdette, D. et al. (2019) Impact of mindfulness-based stress reduction for people with multiple sclerosis at 8 weeks and 12 months: A randomized clinical trial. Multiple Sclerosis 25(8): 1178-1188	- Data not reported in an extractable format or a format that can be analysed
Seron, P., Oliveros, M. J., Gutierrez-Arias, R. et al. (2021) Effectiveness of telerehabilitation in physical therapy: A rapid overview. Physical Therapy 101(6): pzab053	- Systematic review used as source of primary studies
Sesel, A. L.; Sharpe, L.; Naismith, S. L. (2018) Efficacy of psychosocial interventions for people with multiple sclerosis: A meta-analysis of specific treatment effects. Psychotherapy & Psychosomatics 87(2): 105-111	- Systematic review used as source of primary studies
Shanazari, Z.; Marandi, S. M.; Minasian, V. (2013) Effect of 12-week pilates and aquatic training on fatigue in women with multiple sclerosis. Journal of Mazandaran University of Medical Sciences 23(98): 257-264	- Study not reported in English

Study	Code [Reason]
Simpson, R., Booth, J., Lawrence, M. et al. (2014) Mindfulness based interventions in multiple sclerosis--a systematic review. BMC Neurology 14: 15	- Systematic review used as source of primary studies
Simpson, Robert; Mair, Frances S.; Mercer, Stewart W. (2017) Mindfulness-based stress reduction for people with multiple sclerosis – a feasibility randomised controlled trial. BMC Neurology 17(1): 94	- Pain outcomes not reported
Simpson, R., Simpson, S., Ramparsad, N. et al. (2020) Effects of Mindfulness-based interventions on physical symptoms in people with multiple sclerosis - a systematic review and meta-analysis. Multiple Sclerosis and Related Disorders 38: 101493	- Systematic review used as source of primary studies
Sivaramakrishnan, A., Hombali, A. S., Shankar, R. et al. (2019) Transcranial direct current stimulation (tDCS) for improving fatigue, motor function, and pain in people with multiple sclerosis. Cochrane Database of Systematic Reviews	- Cochrane systematic review protocol
White, V., Linardon, J., Stone, J. E. et al. (2020) Online psychological interventions to reduce symptoms of depression, anxiety, and general distress in those with chronic health conditions: a systematic review and meta-analysis of randomized controlled trials. Psychological Medicine: 1-26	- Systematic review used as source of primary studies
White-Lewis, S., Johnson, R., Ye, S. et al. (2019) An equine-assisted therapy intervention to improve pain, range of motion, and quality of life in adults and older adults with arthritis: A randomized controlled trial. Applied Nursing Research 49: 5-12	- Population not relevant to this review protocol
Workman, C. D.; Kamholz, J.; Rudroff, T. (2020) Transcranial direct current stimulation (tDCS) for the treatment of a Multiple Sclerosis symptom cluster. Brain Stimulation 13(1): 263-264	- No outcomes of interest *Only 5 days follow up*
Zakrzewska, J. M.; Wu, J.; Brathwaite, T. S. (2018) A systematic review of the management of trigeminal neuralgia in patients with multiple sclerosis. World Neurosurgery 111: 291-306	- Systematic review used as source of primary studies

Study	Code [Reason]
Zhang, J., Yu, J., Tang, X. et al. (2017) Does whole-body vibration have benefits in patients with multiple sclerosis: A systematic review and meta-analysis. International Journal of Clinical and Experimental Medicine 10(7): 9996-10009	- Systematic review used as source of primary studies
Zou, L., Wang, H., Xiao, Z. et al. (2017) Tai chi for health benefits in patients with multiple sclerosis: A systematic review. PLoS ONE 12(2): e0170212	- Systematic review used as source of primary studies
Zucchella, C., Mantovani, E., De Icco, R. et al. (2020) Non-invasive brain and spinal stimulation for pain and related symptoms in multiple sclerosis: A systematic review. Frontiers in Neuroscience 14: 547069	- Systematic review used as source of primary studies

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2005 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 65: Studies excluded from the health economic review

Reference	Reason for exclusion
None	

Appendix K – Research recommendations – full details

K.1 Research recommendation

For adults with MS, including people receiving palliative care, what is the clinical and cost effectiveness of non-pharmacological interventions for pain?

K.1.1 Why this is important

Chronic pain is a huge public health issues and highly prevalent in MS with impact on the ability to do neurological rehabilitation to prevent deterioration of function due to the underlying damage to other functions like motor, coordination, cognition etc. Improvements in pain decrease the degree of disability and decrease resource utilisation. Research is needed to identify clinical and cost effective non-pharmacological interventions.

K.1.2 Rationale for research recommendation

Importance to 'patients' or the population	If non-pharmacological Interventions are shown to offer clinically important benefits to the management of pain for people with MS, at a reasonable cost threshold, then it may be an important modality to improve current practice and enhance clinical outcomes in this patient group. It would also be important to identify whether a reduction in pain also had a positive impact on other symptoms such as fatigue and depression. If specific interventions are identified to be effective, this can support people with MS to choose effective interventions while an increased understanding of optimal strategies can help standardise care and improve patient outcomes.
Relevance to NICE guidance	This research can reduce the existing uncertainty regarding the clinical and cost-effectiveness of non-pharmacological interventions for pain and support decision making in the development of future recommendations.
Relevance to the NHS	A clear recommendation for the non-pharmacological interventions for pain will offer clinicians clearer guidance on best care for people with MS. Increased knowledge of non-pharmacological interventions would improve and standardise care. With the reduction in the use of opioids and gabapentinoids there is a need for better evidence towards non-pharmacological treatment option for pain in MS. Pain services would not need to be specific to MS but could be shared by patients with other conditions.
National priorities	The national service framework for long term conditions supports the early management of symptoms.
Current evidence base	A moderate number of RCTs were identified but the majority were small and pooling of data was

	not possible with only one or very few studies on each intervention.
Equality considerations	Trials should define the population with respect to the degree of disability and the presence of co-morbid conditions.

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K.123 Modified PICO table

Population	Inclusion: Adults (≥18 years) with MS, including people receiving palliative care. Exclusion: Children and young people <18 years).
Intervention	Any non-pharmacological intervention, for example: • Multidisciplinary rehabilitation/programmes • Acupuncture • Self-management programmes • Exercise (for example stretching, standing, splinting, gym prescription, yoga, tai chi, pilates, relaxation) • Lycra garments • Transcutaneous electrical nerve stimulation (TENS) • Scrambler therapy • Psychological based therapies: CBT, hypnosis, • Mindfulness • Hydrotherapy • Complementary therapies (e.g., massage) • TMS (transcranial magnetic stimulation) and direct current stimulation
Comparator	Interventions will be compared to each other, placebo, sham, no treatment or usual care.
Outcome	• Pain intensity using validated pain scales for example Brief Pain Inventory, Visual Analogue Scale and numerical rating scale • Pain reduction for example >30% and 50% pain reduction from baseline • Patient-reported outcome measures, which refer generally to quality of life and the scales of Multiple Sclerosis Quality of Life Inventory (MSQLI); life satisfaction, EQ5D, SF-36 • Adverse effects of treatment. • Adverse events leading to withdrawal or lack of efficacy • Expanded Disability Status Scale (EDSS) • MS Functional Composite or its subscales if not reported (MSFC). • Functional improvement

	• Reduction of care • Mood related outcomes for example validated depression scales and anxiety scales • Changes in sleep quality/sleep related impairments/ sleep disturbance Follow up: • 3 months up to 6 months
Study design	RCT
Timeframe	Medium
Additional information	Shorter follow up may be appropriate for people receiving palliative care Studies should be powered to detect a minimally important difference of 30% reduction in pain

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