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[Intervention Protocol]

Non-pharmacological interventions for chronic pain in multiple sclerosis

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effectiveness and safety of non-pharmacological therapies for the management of chronic pain in pwMS.

Specific effectiveness questions to be addressed by this review include the following:

- Are non-pharmacological interventions (unidisciplinary and/or multidisciplinary rehabilitation) effective in reducing chronic pain in pwMS?
- What type of non-pharmacological interventions (unidisciplinary and/or multidisciplinary rehabilitation) are effective (least and most effective) and in what setting, in reducing chronic pain in pwMS?

BACKGROUND

All technical terms are included in a Glossary found in [Appendix 1](#).

Multiple sclerosis (MS) is a chronic neurological disease characterised by unpredictable patchy inflammation, scarring and demyelination of the central nervous system (CNS). Despite advances in acute MS management, it remains one of the most common causes of neurological disability in young adults, affecting 1.3 million people worldwide ([WHO 2008](#)) and approximately 20,000 persons in Australia ([MS Society 2011](#)). The median es-

timated incidence of MS globally is 2.5 per 100,000 (range of 1.1 to 4) ([WHO 2008](#)), while the prevalence rate is about 30 per 100,000 population (range 5 to 80) ([Trisolini 2010](#); [WHO 2008](#)). It is more common in females (3:1 ratio) and patterns of MS presentation can vary significantly between individuals ([Compston 1998](#); [Detels 1978](#); [Hammond 1988](#)). The exact aetiology of MS is still unclear but it is associated with an abnormal immune response within the central nervous system, possibly an infectious agent ([Kurtzke 1983](#)). There has been more recent literature on environmental factors such as vitamin D deficiency, lower sun exposure and higher latitude being a modifiable risk factor for multi-

ple sclerosis. This is thought to be due to vitamin D having an immunomodulatory effect, but not associated with disease progression (Alharbi 2015). Genetic risk has also been shown in recent literature, indicating an association between HLA-DRB1 and HLA-DR4 genes and MS susceptibility (O’Gormann 2012). MS is associated with long-term physical, cognitive and behavioural disabilities, restriction in participation, medical complications, and symptoms including pain (Khan 2007b; Khan 2013).

According to the International Association of the Study of Pain (IASP), chronic pain is pain presenting continuously or intermittently for at least three months that persists past the normal time of healing (Merskey 1994). Chronic pain impacts on activities of daily living, relationships, and social roles (Archibald 1994; Ehde 2003; Khan 2007a; Svendsen 2003; Warnell 1991), interferes with work (Archibald 1994) and has been associated with increased psychological impairment, such as depression (Ehde 2003). Many psychosocial factors influence adjustment to chronic pain, including pain-related beliefs, coping behaviours, family members’ responses to pain behaviours (Fordyce 1973), psychological distress, and pain-related disability (Jensen 1999). Chronic pain is associated with poorer general health, increased fatigue, and higher rates of healthcare utilization (Blyth 2003; Ehde 2003; Sullivan 1992; Vickrey 1995). It is a significant health problem, impacting working-age populations and causing social disadvantage (Blyth 2003), and estimated cost is approximately \$34 billion per annum in Australia (Blyth 2001).

In persons with MS (pwMS), symptoms such as headache and neuropathic extremity pain, back pain, painful spasms and Lhermitte sign were common and trigeminal neuralgia least common. However, uncertainty remains with regards to their frequency given the heterogeneity of previous studies. Understanding of pain in pwMS remains poor and there is limited knowledge of pain during the disease course, pain prior to disease onset, pain associated with relapses, and longitudinal follow up (Foley 2013).

Description of the condition

Pain can be a significant problem for a substantial proportion of patients with MS (Ehde 2005; Khan 2007a). It is experienced by 42% to 90% pwMS (Clifford 1984; Heckman-Stone 2001; Moulin 1988; Stenager 1991; Vermote 1986) and occurs at all stages of the disease. MS-related pain can cause both acute and chronic symptoms, and is associated with active inflammation, from the MS process itself (central neuropathic pain such as trigeminal neuralgia) and from MS-related complications (tonic spasms, headaches and musculoskeletal problems such as posture and gait anomalies) (Khan 2011). Pain was reported as one of the most severe symptoms in 8% to 32% of pwMS (Albert 1969; Shibasaki 1974; Stenager 1991) and it often co-exists as a mix of acute, paroxysmal and chronic pain in the same or various parts of the body (Von Korff 1992).

Based on the underlying pathophysiological mechanism, MS-related pain can be classified into 5 categories: neuropathic, nociceptive, psychogenic idiopathic and mixed (Truini 2011). Neuropathic pain, defined by the IASP as pain arising directly from a lesion or disease affecting the somatosensory system (Treede 2008) can consist of persistent extremity pain and dysaesthesia, trigeminal neuralgia, and Lhermitte’s phenomenon, defined as a transient sensation related to neck movements felt in the back of the neck, lower back and other parts of the body (Al-Araji 2005). Nociceptive pain, either inflammatory or non-inflammatory, includes musculoskeletal and low back pain that may be posture-related, optic neuritis (Truini 2011), headaches, and treatment-induced pain. Psychogenic pain is difficult to define and refers to somatoform pain associated with psychiatric conditions such as depression and anxiety, or pain behaviours that have evolved in patients with chronic refractory pain. Idiopathic pain includes conditions which are either poorly understood or controversial such as fibromyalgia, interstitial cystitis and atypical facial pain. The term ‘mixed’, not to be confused with ‘co-existing’, encompasses a heterogeneous group of pain with different pathophysiological mechanisms caused by the same disease, in this case, MS. Such examples are painful tonic spasms which may involve unilateral, bilateral or stereotyped involuntary muscle spasms and spasticity pain.

Description of the intervention

In general, pain in MS is treated with pharmacological agents (Cutter 2000; Rog 2005; Rossi 2009; Shakespeare 2009) and non-pharmacological modalities or a combination of both (Saifuddin 2014). For the purpose of this review, non-pharmacological therapies or interventions refer to treatments and management strategies that do not involve the use of medications or surgery (Amatya 2013; Boldt 2011). A wide range of non-pharmacological interventions have been trialed in pwMS for pain management. Previous studies (Heckman-Stone 2001; Khan 2007a; Khan 2013) have found that MS patients in the community setting frequently use non-pharmacological techniques with variable degrees of effectiveness. The non-pharmacological management techniques include: passive strategies such as Transcutaneous Electrical Nerve Stimulation (TENS), heat and/or cold therapy, supportive braces, alternative therapies; and active strategies such as exercise, biofeedback, relaxation, distraction, and psychosocial interventions (Khan 2007a; Khan 2013). The availability of a variety of therapeutic techniques was postulated to empower patients with greater control of their pain management and possibly allow more optimal adaptation to a progressive condition.

How the intervention might work

The underlying mechanisms of pain in MS are unclear and have been linked with the differentiation and disinhibition of central and pain pathways, central nervous system lesions causing hyperexcitability, and increased neuronal (nerve cell) activity at the site of the lesion in the spinal cord (Beric 1998; Boivie 1999; Hans 2003; Lalkhen 2012). Chronic pain may then develop and evolve as a maladaptive response involving neuronal pathways that are affected by internal and environmental influences in a complex interplay that is then perceived in a highly subjective fashion by each individual. It can arise both centrally and peripherally, and may be triggered by either a noxious stimulus or a non-noxious stimulus, or it can also occur spontaneously in the absence of any definable trigger (Boivie 1999; Jensen 1994; Jensen 1999;). Due to this heterogeneity of chronic pain aetiology (cause) amongst pwMS, modalities that act at different sites along the pain processing pathway may have variable degrees of effectiveness (Khan 2011; Lalkhen 2012).

Although the exact role of physiological deconditioning in nociceptive input or perceived pain is not well defined, it is clear that improvement in overall physical function is linked with improvement in psychosocial function and mood (Simmonds 1996), which in turn influences levels of pain. There is evidence that motor control and proprioceptive efficiency are altered, balance is compromised, and reaction times are slower in persons who are unfit or have pain (Harding 1998). TENS and acupuncture attempt to modulate pain from the periphery, whilst dorsal column stimulation intercepts the nociceptive signal at the level of the spinal cord. Cognitive behavioural therapy and other psychotherapies, on the other hand, utilise strategies that modify perception and cognition to enact a positive change in behavior and mood.

Why it is important to do this review

Pain is prevalent in pwMS and tends to increase over time, due to the MS process itself and from MS-related complications, and is associated with a great interference with daily life activities (Khan 2013). Studies of pwMS in the community have demonstrated that those with higher pain grades reported more disability and healthcare visits, and lower quality of life (Khan 2007a). Non-pharmacological therapies are widely used, both in hospital and ambulatory/mobility settings, to improve pain control, coping ability, daily function and quality of life in MS patients. Chronic pain is found to be amenable to multidisciplinary rehabilitation management (Finlayson 2011; Karjalainen 2003; Khan 2007b; Kraft 2005; Saifuddin 2014). Psychological interventions have shown potential beneficial impact on pwMS, including the management of symptoms such as pain and fatigue (Thomas 2006). Further, TENS is commonly trialed for chronic lower back pain in pwMS and hypoalgesic effects (Al Smadi 2007; Warke 2006). Similarly anodal transcranial Direct Current Stimulation (tDCS) has demonstrated effectiveness in reducing central chronic pain in an MS population, with long-term clinical effects (Mori 2010).

There was only one other systematic review on non-pharmacological management in pwMS, which excluded non-spastic and non-trigeminal pain. The study identified the main categories of education, electrical and physical therapy, and found that low frequency TENS had the greatest reduction in pain scores (Jawahar 2014). Limitations of this systematic review were the inclusion of uncontrolled clinical trials and pilot studies and the neglect of other non-pharmacological interventions, such as surgery, acupuncture, massage therapy, thermotherapy and other electrical therapy such as transcranial stimulation (TMS) and tDCS. An updated systematic evaluation of the existing high-quality evidence is therefore needed to determine the effectiveness and safety of all these modalities to provide clinicians clear guidance for clinical decision-making for appropriate pain management.

OBJECTIVES

To assess the effectiveness and safety of non-pharmacological therapies for the management of chronic pain in pwMS.

Specific effectiveness questions to be addressed by this review include the following:

- Are non-pharmacological interventions (unidisciplinary and/or multidisciplinary rehabilitation) effective in reducing chronic pain in pwMS?
- What type of non-pharmacological interventions (unidisciplinary and/or multidisciplinary rehabilitation) are effective (least and most effective) and in what setting, in reducing chronic pain in pwMS?

METHODS

Criteria for considering studies for this review

Types of studies

- All published randomised controlled trials (RCTs), cross-over studies and clinical controlled trials (CCTs) that compare non-pharmacological therapies with a control for managing chronic pain in participants with MS will be included.
 - We will include only trials with a full journal publication.
 - We will include trials with a minimum treatment period of two weeks or more, with greater attention given to studies with a duration of eight weeks or greater.
 - We will exclude studies that are non-randomised, studies of experimental pain, case reports, and clinical observations.

Types of participants

We will include trials if the study population has a confirmed diagnosis of MS based on standard criteria (McDonald 2001) and participants are aged 18 years and older with chronic pain. We will include all studies with participants with 'chronic pain' or participants suffering from pain longer than three months, irrespective of the use of varying definitions for chronicity of pain. We will include studies that recruited participants with the minimum levels of pain on VAS of 3/10.

Studies including participants with other diagnoses will be excluded unless individual data for the pwMS can be obtained either from the published results or through contact with authors.

Types of interventions

All non-pharmacological therapies to manage chronic pain in MS delivered in any settings (inpatient, outpatient, community, or home-based) will be included, including the following.

- Unidisciplinary: physiotherapy, occupational therapy, and individual treatment modalities, thermotherapy such as heat and cold application, psychological and behavioural therapies including cognitive behavioural therapy and hypnosis, relaxation training, yoga, massage, chiropractic manipulation, acupuncture, other alternative and complementary therapies, TMS, TENS, tDCS, dorsal root entry zone (DREZ) lesioning and others.

- Multidisciplinary rehabilitation programmes. In this review, multidisciplinary rehabilitation is defined as any coordinated therapy programme delivered by two or more disciplines (occupational therapy, physiotherapy, exercise physiology, orthotics, other allied health and nursing) in conjunction with medical input (neurologist or rehabilitation medicine physician) that aims to achieve patient-centred goals related to reducing spasticity).

Control interventions that are likely used for comparison with the above mentioned interventions include placebo or sham interventions.

Types of outcome measures

Diverse outcomes are expected, given the varied presentations of pain-related problems and goals of treatment related to pain severity.

Primary outcomes

The primary outcome will determine whether the intervention produces:

- Reduction in pain measured by validated measures, such as a visual analogue scale (VAS) or numerical rating scale (NRS) (Jensen 2001), Likert scale such as the Patient's Global Impression of Change (PGIC, Hurst 2004) or Clinical Global Impression of Change (CGIC, Zaidler 2003) or specific pain

scales such as the McGill Pain Questionnaire (MPQ, Melzack 1975), Short Form McGill Pain Questionnaire (SFMPQ, Melzack 1987), or Brief Pain Inventory (BPI, Cleeland 1989) and others (subjective or objective). We will be using the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) (Dworkin 2008) which are defined as:

1. at least 30% pain relief over baseline (moderate);
2. at least 50% pain relief over baseline (substantial);
3. much improved on Patient Global Impression of Change Scale (PGIC; moderate);
4. very much improved on PGIC (substantial).

Secondary outcomes

In keeping with the multidimensional model of pain, determining whether the change in pain by the intervention affects the other specific outcome(s) measured by validated tools, which include:

- Other symptoms or impairments: e.g. Multiple Sclerosis Spasticity Scale (MSSS-88, Hobart 2006); Modified Ashworth Scale (MAS, Ansari 2009); Fatigue Impacts Scale (FIS, Fisk 1994);
- Functional activity: e.g. Functional Independence Measure (FIM, Granger 1998), Barthel index (BI, Mahoney 1965);
- Psychosocial outcomes: e.g. Beck Depression Inventory (BDI, Beck 1961), Depression, Stress and Anxiety Scale (DASS, Lovibond 1995);
- Restriction in participation/impact on carers: e.g. Caregiver Strain Index (CSI, Robinson 1983);
- Vocational outcomes: e.g. Work Instability Scale (WIS, Gilworth 2003 2003);
- Quality of life: e.g. Multiple Sclerosis Quality of Life (MSQOL 54, Vickrey 1995);
- Withdrawals due to lack of efficacy;
- Outcomes that reflect utilisation of health care resources and associated cost (reported, where possible);
- Participants experiencing any adverse effects;
- Participants experiencing any serious adverse effects which include any untoward medical occurrence or effect that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospital stay, results in persistent or significant disability or incapacity, congenital anomaly or birth defect, is an 'important medical event' that may jeopardise the person or may require intervention to prevent one of the above characteristics or consequences.

Timing of outcome measures

We will divide outcome time points into short-term (up to three months) and long-term (greater than three months) from the start of the intervention, and long-term follow-up after termination of the intervention.

Search methods for identification of studies

We will consider articles in all languages with a view to translation, if necessary.

Electronic searches

The Information Specialist will search the Trials Register of the Cochrane Multiple Sclerosis and Rare Diseases of the CNS Group, which, among other sources, contains trials from:

- Cochrane Central Register of Controlled Trials (CENTRAL) (2016, most recent issue);
- MEDLINE (PubMed) (1966 to current date);
- Embase (Embase.com) (1974 to current date);
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCOhost) (1981 to current date);
- Latin American and Caribbean Health Science Information Database (LILACS) (Bireme) (1982 to current date);
- ClinicalTrials.gov (<https://clinicaltrials.gov/>); and
- World Health Organization (WHO) International Clinical Trials Registry Platform (<http://apps.who.int/trialsearch/>).

The keywords that we will use to search for trials for this review are listed in [Appendix 2](#).

Information on the Group's Trials Register and details of search strategies used to identify trials can be found in the 'Specialised Register' section within the Cochrane Multiple Sclerosis and Rare Diseases of the Central Nervous System Group's [module](#).

In addition we will search the following databases:

- PsycINFO (1980 to current date), ([Appendix 3](#));
- Allied and Complementary Medicine Database (AMED) (1985 to current date) ([Appendix 4](#)); and
- MANTIS/Ovid (for most recent data available) ([Appendix 5](#)).

Searching other resources

We will conduct an expanded search to identify articles potentially missed through the database searches and articles from 'grey literature'. This will include the following:

- related articles feature (via PubMed);
- ProQuest Dissertations and Theses;
- Web of Science for citation of key authors;
- SIGLE (System for Information on Grey Literature in Europe); and
- Contact authors and researchers active in this field.

Data collection and analysis

Selection of studies

Two review authors (BA, JY) will independently screen and short-list all abstracts and titles of studies identified by the search strategy for appropriateness based on the selection criteria. The same review authors (BA, JY) will independently read the abstract of each study from the short-list of potentially appropriate studies for inclusion or exclusion. The full text of the article will be obtained to determine if the study meets the inclusion/exclusion criteria. Papers assessed in full text that do not meet the inclusion criteria will be listed in the 'Characteristics of excluded studies' table with the reasons for exclusion. If no consensus is met about the possible inclusion/exclusion of any individual study, a final consensus decision will be made by discussion with the third author (FK). Review authors will not be masked to the name(s) of the author(s), institution(s) or publication source at any level of the review. Further information will be sought about the method of randomisation and other methodological issues, if required.

Studies with fatal flaws (for instance, withdrawals by more than 40% of the participants or nearly total non-adherence to the protocol or very poor or non-adjusted comparability in the baseline criteria) will be excluded.

Data extraction and management

Two review authors (BA, JY) will independently extract the data from the included trials using a standardised form and enter the data into the RevMan software ([Review Manager 2014](#)). We will extract data on the following:

- year of publication, year the study was undertaken, and geographical location of the study;
- number of participants included, their age, gender, and type of MS;
- information about the type of pain (neuropathic/nociceptive) that is targeted by the study intervention;
- type of study intervention and treatment duration;
- information about the control intervention(s);
- duration of the study recruitment and follow-up time;
- information about adverse events;
- information about withdrawals;
- information whether the study was specifically designed to measure pain in MS;
- information about study quality; and
- measures of treatment effect (outcome measures).

A final check will be made by a third review author (FK). To summarize all data on reduction in pain, the benchmarks of the IMMPACT recommendations for the evaluation of reduction in pain ([Dworkin 2008](#)) will be used.

We will summarise all studies that meet the inclusion criteria in the 'Characteristics of included studies' table.

Assessment of risk of bias in included studies

Two review authors (BA, JY) will independently assess the methodological quality of the included studies using the 'Risk of bias' tool outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will assess the following for each study.

1. Random sequence generation (checking for possible selection bias). We will assess the method used to generate the allocation sequence as: low risk of bias (any truly random process, random number table, computer random generator) and unclear risk of bias (when the method is not clearly stated). We will exclude studies with a non-random process.

2. Allocation concealment (checking for possible selection bias). The method used to conceal the allocation to interventions prior to assignment determines whether the intervention allocation could have been foreseen in advance, during recruitment, or changed after assignment. We will assess methods as low risk of bias (telephone or central randomisation; consecutively numbered, sealed, opaque envelopes) or unclear risk of bias (when method is not clearly stated). We will exclude studies that did not conceal allocation.

3. Blinding of participants, personnel, and outcome assessment (checking for possible performance bias and detection bias). We will assess the methods used to blind study participants, personnel, and outcome assessors from knowledge of which intervention a participant received. We will assess methods as low risk of bias (study states it was blinded and described the method used to achieve the blinding) or unclear risk of bias (study stated it was blinded but did not provide adequate description of how this was achieved). We will exclude studies that were not double blinded.

4. Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data). We will assess the methods used to deal with incomplete data as low risk of bias (fewer than 10% of participants did not complete the study or used 'baseline observation carried forward' analysis or both), unclear risk of bias (used 'last observation carried forward' analysis) or high risk of bias (used 'completer' analysis).

5. Size of study (checking for possible studies confounded by small size). We will assess methods as being at low risk of bias (200 participants or more per treatment arm), unclear risk of bias (50 to 199 participants per treatment arm) or high risk of bias (fewer than 50 participants per treatment arm).

Any disagreements or lack of consensus will be resolved by a third review author (FK).

Assessment of the quality of the evidence

We will assess the quality of the body of evidence using the GRADE approach as outlined in the GRADE handbook (GRADE Working Group 2004), relating to the following outcomes for the main comparisons:

- pain (severity, grade);

- quality of life;
- other symptoms or impairments: e.g. spasticity, fatigue;
- functional activity; and
- psychosocial outcomes.

We will use the GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group approach (Guyatt 2008) in order to create 'Summary of findings' tables. We will include key information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on the main outcomes.

The GRADE system uses the following criteria for assigning grade of evidence.

- High = further research is very unlikely to change our confidence in the estimate of effect.
- Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low = any estimate of effect is very uncertain.

We will decrease the grade if there is:

- serious (-1) or very serious (-2) limitation to study quality;
- important inconsistency (-1);
- some (-1) or major (-2) uncertainty about directness;
- imprecise or sparse data (-1);
- high probability of reporting bias (-1),

We will increase the grade if there is:

- strong evidence of association - significant relative risk of > 2 (< 0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1);
- very strong evidence of association - significant relative risk of > 5 (< 0.2) based on direct evidence with no major threats to validity (+2);
- evidence of a dose response gradient (+1);
- all plausible confounders would have reduced effect (+1).

Measures of treatment effect

All quantitative data will be entered and analysed in the RevMan software (Review Manager 2014). For each outcome of interest, summary estimates of treatment effect (with 95% confidence interval (CIs)) for each comparison will be calculated. Where possible, risk ratios (RR) with 95% CIs for dichotomous data will be calculated, while difference in means or standardised difference in means (SMD) with 95% CIs for continuous data will be calculated. The results of individual studies will be discussed and presented in table and graphical format, where data aggregation is not possible.

Unit of analysis issues

We anticipate that the appropriate unit of analysis will be type, intensity, and setting of non-pharmacological interventions. A qualitative analysis using GRADE for existing evidence will be attempted in any event (Higgins 2011). Trials with multiple observations for the same outcome will be assessed according to randomisation and types of interventions, and we will perform separate analyses based on different periods. Studies with parallel groups will be included, but only data from the first phase of cross-over trials will be included, due to the potential carry-over effects in the second phase.

Dealing with missing data

If insufficient data are available, the study will be reported but not included in the final analysis. There will be analysis of the available data only and we will assume the data are missing at random.

Assessment of heterogeneity

We will conduct statistical analysis, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will assess clinical heterogeneity by examining the characteristics of the studies, the similarity between the types of participants, the interventions and the outcomes, as specified in the criteria for included studies. To check for statistical heterogeneity between studies, both the I^2 statistic and the Chi^2 test of heterogeneity will be used, as well as visual inspection of the forest plots.

The presence of substantial heterogeneity as indicated by an $I^2 > 50\%$ will be considered. A fixed-effect meta-analysis will be used if the $I^2 \leq 50\%$; if the $I^2 > 50\%$, the individual trial characteristics will be explored to identify potential sources of heterogeneity, using pre-planned subgroup analyses. Meta-analysis using both fixed-effect and random-effects modelling will be performed, where there is substantial heterogeneity to assess sensitivity to the choice of modelling approach. The most conservative outcome will be reported, if there are non-identical results.

Assessment of reporting biases

Publication bias will be minimized by performing comprehensive searches of multiple databases (Egger 1998). Where data are not reported in full for certain outcomes, authors will be contacted for the full data set or the reason for not publishing the data. If we identify sufficient studies (at least 10), potential biases of

reporting will be assessed using funnel plots and visual inspection for asymmetry according to the approach outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Data synthesis

We will pool results from clinically similar studies for the meta-analysis, if sufficient studies are available. We will attempt a quantitative analysis if there is clinical homogeneity and the methods and available data in each study allow. If appropriate, a weighted treatment effect will be calculated across studies, using RevMan software (Review Manager 2014). The results will be expressed as risk ratios (RRs) with 95% confidence intervals (CIs) and risk differences (RDs) with 95% CIs for dichotomous outcomes and standard mean differences (SMDs) with 95% CIs for continuous outcomes.

Subgroup analysis and investigation of heterogeneity

Treatment effects in subgroups of trials will be analysed and compared. If data are available, we will perform subgroup analysis for the following:

- sex (male/female);
- type of MS (relapsing remitting, progressive);
- EDSS (< 6, > 6);
- duration of follow-up of the participants (three months; > three months);
- type of non-pharmacological intervention (unidisciplinary and/or multidisciplinary rehabilitation); and
- settings (i.e. inpatient, ambulatory care, community).

Sensitivity analysis

We plan no sensitivity analysis because the evidence base is known to be too small to allow reliable analysis; we will not pool results from chronic pain of different central origins in the primary analyses.

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* Indicates the major publication for the study

APPENDICES

Appendix I. Glossary

- **Dorsal column:** spinal pathways located at the rear of the spinal cord
- **Dysesthesia:** an unpleasant abnormal sensation that can occur spontaneously or when touched; the sensation can be felt as pain, burning, wetness, itching, electric shock or ‘pins and needles’
- **Fibromyalgia:** condition characterised by widespread pain; the cause is unknown
- **Hypoalgesia:** reduced experience of pain to a normally painful stimulus
- **Idiopathic pain:** pain with a cause that cannot be identified
- **Interstitial cystitis:** a long-term painful bladder condition also known as ‘painful bladder syndrome’ or ‘bladder pain syndrome’
- **Lhermitte sign:** a brief electric shock or vibration which runs from the neck down the spine and is uncomfortable
- **Neuropathic pain:** pain arising because of disease in the nervous system
- **Nociceptive pain:** pain caused by tissue damage, usually described as a sharp, aching, or throbbing pain.
- **Optic neuritis:** inflammatory damage to optic nerve (nerve from brainstem) that may lead to complete or partial loss of vision
- **Paroxysmal:** a sudden occurrence or intensification of symptoms
- **Proprioception:** the perception of outside stimuli that informs the body of the relative position of its parts
- **Psychogenic pain:** physical pain that is caused, increased, or prolonged by mental, emotional, or behavioural factors
- **Refractory:** a disease or condition which does not respond to attempted forms of treatment, for example poor pain of relief after pain-relieving medicine
 - **Somatosensory:** sensory system in the body involved in detecting touch, pressure, pain, temperature, movement and vibration
 - **Thermotherapy:** application of heat or cold to the body for pain relief
 - **Tonic spasms:** sudden abnormal muscle contraction
 - **Transcranial direct cranial stimulation:** non-invasive brain stimulation using low currents
 - **Transmagnetic stimulation:** application of brief magnetic pulses that stimulate the brain
 - **Trigeminal neuralgia:** nerve pain involving the trigeminal nerve which is responsible for sensation in the face and for controlling biting and chewing

Appendix 2. Keywords

{Pain} OR {chronic pain} OR {pain management} OR {pain intractable} OR {pain measurement} OR {pain threshold} OR {nociceptors} AND {rehabilitation } OR {exercise} OR {exercise therapy} OR {physical therapy} OR {psychotherapy} OR {hydrotherapy} OR {complementary therapies} OR {transcutaneous electric nerve stimulation} OR {transcranial magnetic stimulation} OR {dorsal column stimulation} OR {spinal cord stimulation} OR {peripheral field stimulation} OR {dorsal root entry zone lesion} OR {DREZ}

Appendix 3. PsycINFO

S1 TX multiple sclerosis
S2 DE "Multiple Sclerosis"
S3 TX demyelinating disease*
S4 DE "Demyelination"
S5 TX transverse myelitis
S6 DE "Myelitis"
S7 TX neuromyelitis optica
S8 TX optic neuritis
S9 TX encephalomyelitis acute disseminated
S10 DE "Encephalopathies"
S11 TX devic
S12 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11
S13 DE "Somatosensory Disorders"
S14 DE "Pain" OR DE "Aphagia" OR DE "Back Pain" OR DE "Chronic Pain" OR DE "Headache" OR DE "Myofascial Pain" OR DE "Neuralgia" OR DE "Neuropathic Pain" OR DE "Somatoform Pain Disorder"
S15 TX pain
S16 TX central pain
S17 TX dys#esthesia or TX dys#esthetic
S18 S13 or S14 or S15 or S16 or S17
S19 TX intractable
S20 DE "Pain Measurement"
S21 DE "Pain Perception"
S22 DE "Pain Thresholds" or DE "Pain Management"
S23 DE "Nociceptors"
S24 AB pain N5 (refer* or refractory or intractable or receptor* or nocicept* or muskuloskeletal or chronic or intens* or threshold* or shoulder* or abdominal* or back or neuropath*)
S25 TI pain N5 (refer* or refractory or intractable or receptor* or nocicept* or muskuloskeletal or chronic or intens* or threshold* or shoulder* or abdominal* or back or neuropath*)
S26 (TI nocicept* N3 neuron*) OR TI pain*
S27 S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26
S28 S12 and S18 and S27
S29 DE "Rehabilitation" OR DE "Cognitive Rehabilitation" OR DE "Neuropsychological Rehabilitation" OR DE "Neurorehabilitation" OR DE "Occupational Therapy" OR DE "Physical Therapy" OR DE "Psychosocial Rehabilitation"
S30 DE "Exercise" OR DE "Aerobic Exercise" OR DE "Weightlifting" OR DE "Yoga"
S31 TX exercise therap* or TX stretching or TX tai chi or TX yoga
S32 DE "Psychotherapy" OR DE "Adlerian Psychotherapy" OR DE "Adolescent Psychotherapy" OR DE "Analytical Psychotherapy" OR DE "Autogenic Training" OR DE "Behavior Therapy" OR DE "Brief Psychotherapy" OR DE "Child Psychotherapy" OR DE "Client Centered Therapy" OR DE "Cognitive Behavior Therapy" OR DE "Conversion Therapy" OR DE "Eclectic Psychotherapy" OR DE "Emotion Focused Therapy" OR DE "Existential Therapy" OR DE "Experiential Psychotherapy" OR DE "Expressive Psychotherapy" OR DE "Eye Movement Desensitization Therapy" OR DE "Feminist Therapy" OR DE "Geriatric Psychotherapy" OR DE "Gestalt Therapy" OR DE "Group Psychotherapy" OR DE "Guided Imagery" OR DE "Humanistic Psychotherapy" OR DE "Hypnotherapy" OR DE "Individual Psychotherapy" OR DE "Insight Therapy" OR DE "Integrative Psychotherapy" OR DE "Interpersonal Psychotherapy" OR DE "Logotherapy" OR DE "Narrative Therapy" OR DE "Persuasion Therapy" OR DE "Primal Therapy" OR DE "Psychoanalysis" OR DE "Psychodrama" OR DE "Psychodynamic Psychotherapy" OR DE "Psychotherapeutic

Counseling” OR DE “Rational Emotive Behavior Therapy” OR DE “Reality Therapy” OR DE “Relationship Therapy” OR DE “Solution Focused Therapy” OR DE “Supportive Psychotherapy” OR DE “Transactional Analysis”

S33 TX cognitive behavior#ral or TX relaxation or TX breathing or TX hypnosis

S34 DE “Relaxation” OR DE “Relaxation Therapy” OR DE “Progressive Relaxation Therapy”

S35 DE “Hypnosis” OR DE “Autohypnosis”

S36 TX hydrotherap* or TX thermo* or TX heat or TX warm or TX cold or TX cool

S37 DE “Alternative Medicine”

S38 DE “Acupuncture” OR DE “Aromatherapy” OR DE “Massage” OR DE “Medicinal Herbs and Plants” OR DE “Meditation” OR DE “Osteopathic Medicine”

S39 TX massage or TX chiropractic or TX manipulation or TX acupuncture or TX acupressure or TX osteopath* or TX homeopath* or TX naturopath* or TX aromathera* or TX art or TX music or TX alternative or TX complementary or TX CAM

S40 TX transcutaneous electrical stimulation

S41 DE “Electrical Stimulation” OR DE “Electrical Brain Stimulation” OR DE “Electroconvulsive Shock”

S42 DE “Transcranial Magnetic Stimulation”

S43 TX transcranial magnetic stimulation

S44 TX dorsal column stimulation

S45 TX spinal cord stimulation

S46 TX peripheral field stimulation

S47 TX dorsal root entry zone lesion*

S48 TX DREZ

S49 DE “Osteopathic Medicine”

S50 TX orthotics or TX orthosis or TX brace*

S51 TX nonpharmaco* or TX non-pharmaco*

S52 S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51

S53 S28 and S52

S54 AB randomi#ed OR TI randomi#ed

S55 DE “Clinical Trials”

S56 AB placebo

S57 AB randomly

S58 TI trial

S59 S53 or S54 or S55 or S56 or S57 or S58

S60 S59 and S53

Appendix 4. AMED

S1 TX multiple sclerosis

S2 (DE “MULTIPLE SCLEROSIS”)

S3 TX demyelinating disease*

S4 TX transverse myelitis

S5 TX neuromyelitis optica

S6 TX optic neuritis

S7 TX encephalomyelitis acute disseminated

S8 (DE “ENCEPHALOMYELITIS”)

S9 TX devic

S10 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9

S11 (DE “PARESTHESIA”)

S12 (DE “PAIN”)

S13 TX pain

S14 TX central pain

S15 TX dys#esthesia or TX dys#esthetic

S16 S11 or S12 or S13 or S14 or S15

S17 (DE "PAIN INTRACTABLE")
 S18 (DE "PAIN MEASUREMENT")
 S19 (DE "PAIN THRESHOLD")
 S20 TX nociceptor*
 S21 AB pain N5 (refer* or refractory or intractable or receptor* or nocicept* or muskuloskeletal or chronic or intens* or threshold* or shoulder* or abdominal* or back or neuropath*)
 S22 TI pain N5 (refer* or refractory or intractable or receptor* or nocicept* or muskuloskeletal or chronic or intens* or threshold* or shoulder* or abdominal* or back or neuropath*)
 S23 (TI nocicept* N3 neuron*) OR TI pain*
 S24 S17 or S18 or S19 or S20 or S21 or S22 or S23
 S25 S10 and S16 and S24

Appendix 5. MANTIS/Ovid

1 multiple sclerosis.mp.
 2 multiple sclerosis.sh.
 3 demyelinating disease*.mp.
 4 demyelinating diseases.sh.
 5 transverse myelitis.mp
 6 myelitis, transverse.sh.
 7 neuromyelitis optica.mp
 8 optic neuritis.mp
 9 optic neuritis.sh
 10 encephalomyelitis acute disseminated.mp
 11 encephalomyelitis, acute disseminated.sh
 12 devic.mp
 13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
 14 paresthesia.sh
 15 pain.sh
 16 pain.mp
 17 central pain.mp
 18 (dys?esthesia or dys?esthetic).mp.
 19 14 or 15 or 16 or 17 or 18
 20 pain, intractable.sh
 21 pain measurement.sh
 22 pain threshold.sh
 23 nociceptors.sh.
 24 (pain adj5 (refer* OR refractory OR intractable OR receptor* OR nocicept* OR muskuloskeletal OR chronic OR intens* OR threshold* OR shoulder* OR abdominal* OR back OR neuropath*)).ab,ti.
 25 ((nocicept* adj3 neuron*) OR pain*).ti.
 26 20 or 21 or 22 or 23 or 24 or 25
 27 13 or 19 or 26

CONTRIBUTIONS OF AUTHORS

Bhasker Amatya (BA) and Fary Khan (FK) were involved in all aspects of the protocol. Comments from Jamie Young (JY) were incorporated into the drafts. All authors will be involved at the review stage.

DECLARATIONS OF INTEREST

The authors are clinicians in the field of Physical and Medical Rehabilitation who wish to provide the best possible service to their patients.

BA: has no personal or financial conflicts of interest in the findings of this review.

JY: has no personal or financial conflicts of interest in the findings of this review.

FK: has no personal or financial conflicts of interest in the findings of this review.

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