Non-pharmacological Management of Chronic Pain in Multiple Sclerosis and Rehabilitation Outcomes

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Abstract

Multiple sclerosis (MS) is a chronic, inflammatory and demyelinating autoimmune condition which affects the central nervous system. Multiple sclerosis can present with a wide variety of symptoms and can affect a patient’s mobility, sensory and cognitive functions. Pain in multiple sclerosis is common and can present as either acute or chronic pain. Chronic pain is pain which lasts greater than 3-6 months and has significant implications on a patient’s health, disability and quality of life. Causes for chronic pain in MS can range from nociceptive somatic pain to neuropathic pain and specific chronic pain syndromes which include trigeminal neuralgia and peripheral neuropathy. Currently, there is a lack of literature on chronic pain in multiple sclerosis.

Given the prevalence of pain, its significant impact on patients and the need for greater evidence for non-pharmacological interventions, further information is required to help with improving identification, assessment and management of chronic pain in multiple sclerosis. In this thesis, four studies address current gaps in the literature and help progress evidence-based practice.

Study 1 is a systematic review of the effectiveness of non-pharmacological management of chronic pain in multiple sclerosis. Despite there being very low quality of evidence, it remains unknown what type of non-pharmacological interventions reduce the intensity of chronic pain and improve quality of life and function in multiple sclerosis. This study acknowledges the gaps in the current research, the inherent difficulties associated with the review of non-pharmacological interventions, methodological limitations and appropriate study designs.

Study 2 is a 10-year longitudinal study on chronic pain in multiple sclerosis in an Australian cohort. This study showed that over time there was a greater representation of bilateral bodily pain, greater subjective worse pain and deterioration in the quality of life and increase in carer burden. This study suggests that over-time chronic pain is persistent and has a significant impact on people with multiple sclerosis.

Study 3 is a retrospective study on the effectiveness of interdisciplinary management of chronic pain in multiple sclerosis and central nervous system disorders. This study accessed clinical data from an Australian and New Zealand-based electronic pain clinic database. From this database; patient outcomes were compared between those with multiple sclerosis and central nervous system disorders and those without these comorbidities. This study showed that those with multiple sclerosis and central nervous system disorders could also benefit from interdisciplinary management and have improvements pain severity scores, catastrophisation, depression, anxiety and stress scores and improvement in pain self-efficacy.

Study 4 is a prospective single-blinded randomised controlled trial using transcranial direct stimulation for chronic neuropathic pain in multiple sclerosis. This study showed that those who had received transcranial direct stimulation compared to sham treatment had an improvement in pain visual analogue scale but no change in affective outcome measures, quality of life scores and depression, anxiety and stress scores. In addition to this; the most common adverse effect was mild tingling which was only during stimulation. This study suggests that transcranial direct stimulation is
a safe and feasible non-pharmacological intervention for chronic neuropathic pain in multiple sclerosis.

This work was completed to test the hypothesis that non-pharmacological interventions can improve patient outcomes. The study conclusions can help with evidence-based recommendations, future-research directions and clinical implementation of non-pharmacological interventions.
Declaration

This declaration is to certify that:

1. The thesis comprises only my original work towards the PhD except where indicated in the Preface.

2. Due acknowledgement has been made in the text to all other material used.

3. The thesis is fewer than 100000 words in length, exclusive of tables, maps, bibliographies and appendices.

The study was not funded, and there are no conflicts of interest to declare.

Jamie Young
Preface

I certify that this thesis is my original work. I am incredibly grateful to my colleagues who provided assistance and support in the following areas.

- Fary Khan—advice, design and plan of research studies, and review of all chapters
- Mary Galea—advice, research design, review of all sections, and supply of equipment
- Maryam Zogra—advice, research design, review of chapters, supervision of study implementation
- Judy Savage—advice and external support
- Bhasker Amatya—advice, research design, review of sections, statistical support

Multi-author papers

Copies of the four multi-author publications arising from this thesis are presented in Appendix 1. The contributions of the co-authors are listed below:

- Bhasker Amatya—advice, study design, appraisal of included studies and review of the manuscript
- Fary Khan—advice, study design, appraisal of included studies and evaluation of the manuscript

- Bhasker Amatya—advice, statistical support and review of the manuscript
- Mary Galea—advice, revision of the manuscript
- Fary Khan—advice, study design and review of the manuscript

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- Steven Mantopoulos—advice, study design and review of the manuscript
- Malcolm Hogg—advice and revision of the manuscript
- Fary Khan—advice and review of the manuscript
- Hilarie Tardiff—advice, study design and review of the manuscript
- Megan Blanchard—advice, statistical analysis and review of the manuscript
- Mary Galea—advice and revision of the manuscript

The Effect of Transcranial Direct Current Stimulation on Chronic Neuropathic Pain in Patients with Multiple Sclerosis: Randomised Controlled Trial (Under review –Pain Medicine)
Maryam Zogra—advice, study design, supervision of intervention and review of the manuscript
- Mary Galea—advice, the supply of equipment and review of the manuscript
- Fary Khan—advice and review of the manuscript
Conflicts of Interest
None to declare
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I acknowledge the guidance, support and advice of my primary supervisor, Professor Fary Khan, who has supported me along the way to complete my thesis. I want to thank my other supervisors including Professor Mary Galea, Dr Maryam Zoghi and Professor Judy Savage, who have also given me support. I appreciate all my supervisors for their overall supervision and help.

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List of Publications (Peer-reviewed)


Young J, Mantopoulos S. Blanchard M, Tardif H, Hogg M, Khan F, Galea MP. Non-pharmacological Management of Chronic Pain in Multiple Sclerosis (Accepted for publication- International Journal of Therapy and Rehabilitation 2019)
Glossary

**Chronic pain**
Chronic pain is defined by the International Association of the Study of Pain as pain that persists for more than three months.

**Multiple Sclerosis**
The International Classification of Diseases defines multiple sclerosis as a progressive autoimmune disorder affecting the central nervous system resulting in demyelination. Patients develop physical and cognitive impairments that correspond to the affected nerve fibres.

**Interdisciplinary management**
A team approach involving team members from different disciplines working collaboratively with a common purpose, to set goals, make decisions and share resources and responsibilities.

**Non-pharmacological interventions**
Non-pharmacological interventions are therapies or interventions that do not involve the use of medications or surgery.

**Transcranial direct stimulation**
Transcranial direct stimulation is a non-invasive brain stimulation that uses direct electrical currents to stimulate specific parts of the brain.
Abbreviations

AQol Assessment of Quality of Life
BPI Brief Pain Inventory
CCT clinical controlled trial
CGRP calcium gene-related peptide
CPG Chronic Pain Grade
CSI Carer Strain Index
DASS Depression, Stress and Anxiety Scale
DLPFC dorsolateral prefrontal cortex
EAE experimental autoimmune encephalomyelitis
ePPOC electronic persistent pain outcomes collaboration
GRADE Grades of Recommendation, Assessment, Development and Evaluation
HREC Human Research and Ethics Committee
IMMPACT Initiative on methods, measurement and pain assessment in clinical trials
M1 primary motor cortex
MS multiple sclerosis
MSQOL 54 Multiple Sclerosis Quality of Life
NMDA N-methyl-D-aspartate
NPS Neuropathic Pain Scale
PCS Patient Catastrophizing Scale
PSEQ Patient Self Efficacy Questionnaire
QoL Quality of Life
QST quantitative sensory testing
RCT randomised controlled trial
RMH Royal Melbourne Hospital
S1 somatosensory cortex
SAS Statistical analysis software
SD Standard deviation
SFMPQ Short-form Mcgill Questionnaire
tDCS transcranial direct stimulation
TENS transcutaneous electrical nerve stimulation
tRNS transrandom noise stimulation
TRP transient receptor potential
VAS Visual Analogue Scale
Chapter 1. Thesis Introduction

This thesis will investigate the effectiveness of non-pharmacological interventions for chronic pain in multiple sclerosis (MS). This section will review:

- The overview of the current literature.
- Current understanding of nociception and pain.
- Understanding of chronic pain in MS.
- History of the research on chronic pain in MS.
- The significance of chronic pain in MS and its impact.
- The effects of transcranial direct stimulation.
- Gaps in the literature.
- The need for further development in this area.

1.1. Overview of Chronic Pain in Multiple Sclerosis

Multiple sclerosis (MS) is a chronic inflammatory and demyelinating autoimmune condition which affects the central nervous system (1). Studies estimate in Australia that there are 23,700 people with MS (0.1%) and 2,500,000 worldwide (2). MS can present with a wide variety of symptoms and can affect a patient’s mobility, sensory and cognitive functions. Common symptoms include muscle weakness, paraesthesia, visual disturbances, imbalance and even pain (3). Pain is defined by the International Association Study of Pain (IASP) as an unpleasant emotional and sensory experience by actual or potential tissue damage or described in such terms (4). People with MS commonly experience chronic pain (defined as pain greater than three months) and is difficult to treat (5).

A review of the current literature shows that chronic pain is an underreported but a significant symptom in MS (6). Studies have shown the prevalence ranges from 23% to 90% (7), and this wide range is due to different methodologies, study designs, sample sizes and variations in criteria used to classify pain in MS (6). However, this figure is still significantly high especially in a population which has a concurrent disability (6). Longitudinal studies have also shown that chronic pain is persistent in these individuals with a prevalence rate of 75% compared to 46% initially in the Italian population over five years (8). Another longitudinal study, in an Australian population, showed there was an increase in participants complaining of chronic pain from 65% to 79% over seven years (9).

1.1.1. Causes of Chronic Pain in Multiple Sclerosis

There is a range of different pathophysiological mechanisms associated with chronic pain in MS (10). Understanding the underlying mechanisms is helpful, and chronic pain in MS is commonly classified into nociceptive, neuropathic and mixed pain as represented in Table 1 (11). There are chronic pain syndromes often associated with MS which include headaches, optic neuritis, painful tonic spasms (involuntary muscle contractions), trigeminal neuropathic pain (neuropathic pain on flexion of the neck and lhermitte's phenomenon (a paroxysmal electric sensation that occurs in the facial or oral regions) (12). Studies have shown that headaches are the most common type of pain in MS and the reported lifetime prevalence of 64%-70.5% (13). Neuropathic pain is the next most common pain-type
characterised most frequently by extremity pain with an estimated lifetime prevalence range from 12% to 28% (14). Nociceptive pain which is marked by musculoskeletal pain, postural anomalies and non-specific back pain has a lifetime prevalence of 10 to 16% (11). Other chronic pain syndromes such as trigeminal neuralgia have an estimated prevalence of 3.8% (15) and are frequently related to MS and painful tonic spasms which have an estimated lifetime prevalence of 11% (16).

<table>
<thead>
<tr>
<th>Pain classification</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous CNP</td>
<td>Dysaesthetic extremity pain</td>
</tr>
<tr>
<td>Intermittent CNP</td>
<td>Lhermitte’s sign</td>
</tr>
<tr>
<td></td>
<td>Trigeminal neuralgia</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>Painful tonic spasms</td>
</tr>
<tr>
<td></td>
<td>Low back pain</td>
</tr>
<tr>
<td></td>
<td>Muscle spasms</td>
</tr>
<tr>
<td>Mixed neuropathic and non-neuropathic pain</td>
<td>Headache</td>
</tr>
</tbody>
</table>

Table 1. Classification of pain in multiple sclerosis (adapted from “Pain associated with multiple sclerosis: systematic review and proposed classification”, by O’Connor AB et al. Pain. 2008; 137(1):96-111)

A classification of pain in MS by characteristic.

Legend: CNP=chronic neuropathic pain (17).

1.1.2. Impact of Chronic pain in Multiple Sclerosis

Chronic pain in MS has a significant impact on multiple levels including individuals and the wider community (9). A study on the impact of chronic pain in MS found a significant impact on work, sleep and relationships (18). In addition to this, there is also evidence for increased fatigue, lower physical activity and a high chronic pain grading score which relates to increased disability due to pain [9]. Studies show an association between chronic pain in MS and mental health issues such as anxiety and depression (19). Studies report that 6%-19% of patients with MS have pain and depression which co-occurred (19) and can enhance the severity of pain and impact on quality of life and treatment efficacy (19).

1.1.3. Models of Chronic Pain in Multiple Sclerosis

Although a biomedical approach remains the mainstay for treatment of chronic pain in MS; management of chronic pain must also involve a multidisciplinary approach (20). The literature has proposed multiple models for pain over the years. One of the original models of pain was a model by Descartes in 1664 which was a purely biomedical model focusing on nociception, pain fibres and pain perception but did not take into account the holistic experience of pain. (21). Later on, Melzack and
Casey proposed another model of pain published in 1968 which described pain regarding three dimensions including sensory-discriminatory, motivational-affective and cognitive evaluative (22). The pain was described in this model as an interaction between these domains and noted that pain was not only managed from the perspective of a physiological dimension but also on a motivation-affective and cognitive-dimension level. Appropriate pain management required all these dimensions need to be addressed to be effective (21). A more recent and contemporary pain model is one proposed by Loeser, as shown in Figure 1, which supports the idea that pain is more than just a physiological basis. This model highlights the complexity of chronic pain through an ‘onion model’ and places nociception (a response to a harmful stimulus) within overlying interactions with pain (sensory), suffering (affective) and pain behaviours (22).

![Loeser model of pain](adapted from “History of Pain: The Nature of Pain”, by Olson KA, Practical Pain Management 2013)

An example of the Loeser Model of Pain. This model is based on overlying circles that are linear. It starts with a physiological stimulus that leads to pain, resulting in suffering and finally antalgic behaviours (23).

A key concept to address in models of pain is the distinction between nociception and pain. Nociception occurs when nociceptors detect noxious stimuli and is defined as the encoding and processing of potentially harmful stimuli in the nervous system (24). Typically; nociception occurs due to tissue injury and detected by nociceptors in the peripheral structures (25). These nerve endings then transmit to the dorsal horn of the spinal cord, nucleus caudalis, thalamic tract, the brain stem and
then ultimately the cerebral cortex (26). Pain is the result of higher brain processing whereas nociception can occur in the absence of pain (27).

The anatomical basis for nociception has been studied in the literature and forms the basis of pain perception and neuroanatomy. Nociceptors are receptors in the tissue which are activated specifically by noxious stimuli (28). Nociceptors are classified as mechanical, thermal, chemical, mixed, polymodal and silent receptors and commonly located in the skin, muscles, tendons, joints, meninges and viscera. Interestingly, there are no nociceptors situated in the central nervous system (28). The nociceptors are free nerve endings and contain transient receptor potential (TRP) channels that are similar to sodium and potassium channels which transduce noxious stimuli to initiate action potentials (29). Other ligand-gated channels include the acid-sensing ion channels, voltage-gated sodium channels, and potassium and calcium channels (30). The location of the cell bodies of the nociceptors exists in the dorsal root ganglion for the trunk, limbs and viscera and the trigeminal neuralgia for the head, neck and oral cavity (31). Common signalling molecules and ligands for nociception work on different ionotropic and metabotropic receptors and common neurotransmitters include glutamate, substance P, calcium gene-related peptide (CGRP), galanin and somatostatin as shown in Table 2 (32).

<table>
<thead>
<tr>
<th>Ionotropic receptor</th>
<th>Subtype</th>
<th>Ligand</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRP</td>
<td>TRPV1</td>
<td>heat (≥43°C, unsensitised), capsaicin, H⁺ (protons)</td>
</tr>
<tr>
<td></td>
<td>TRPV2</td>
<td>heat (≥52°C)</td>
</tr>
<tr>
<td></td>
<td>TRPV3, TRPV4</td>
<td>warm (32–39°C)</td>
</tr>
<tr>
<td></td>
<td>TRPM8</td>
<td>cool (≤26°C)</td>
</tr>
<tr>
<td></td>
<td>TRPA1</td>
<td>environmental irritants (mustard oil, nicotine, formaldehyde, acrolein)</td>
</tr>
<tr>
<td>acid sensing</td>
<td>ASIC1-4, TRAAK/TREK</td>
<td>H⁺ (protons)</td>
</tr>
<tr>
<td>glutamate</td>
<td>NMDA, AMPA Kainate, GlurR1-5, NR1-2</td>
<td>glutamate</td>
</tr>
<tr>
<td>purine</td>
<td>P2X1-6</td>
<td>ATP</td>
</tr>
<tr>
<td>serotonin</td>
<td>5-HT3</td>
<td>5-HT</td>
</tr>
<tr>
<td>nicotinic</td>
<td>nACh (multiple subtypes)</td>
<td>acetylcholine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabotropic receptor</th>
<th>Subtype</th>
<th>Ligand</th>
</tr>
</thead>
<tbody>
<tr>
<td>metabotropic glutamate</td>
<td>mGluR_12,5</td>
<td>glutamate</td>
</tr>
<tr>
<td>prostanoids</td>
<td>EP₁,₂</td>
<td>PGE₂ (prostaglandins)</td>
</tr>
<tr>
<td></td>
<td>EP₃</td>
<td>PG₁₂ (prostacyclin)</td>
</tr>
<tr>
<td>histamine</td>
<td>H₁</td>
<td>HA</td>
</tr>
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<td>serotonin</td>
<td>5-HT₁,₂, 5-HT₂a, 5-HT₃</td>
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<td>bradykinin</td>
<td>B₁, B₂</td>
<td>BK</td>
</tr>
<tr>
<td>cannabinoid</td>
<td>CB₁, CB₂</td>
<td>anandamide</td>
</tr>
<tr>
<td>tachykinin</td>
<td>neurokinin-1 (NK₁)</td>
<td>substance P, neurokinin A</td>
</tr>
<tr>
<td>proteinase</td>
<td>PAR₁,₂</td>
<td>protease</td>
</tr>
<tr>
<td>tyrosine kinase receptor</td>
<td>TrkA, p75 neurotrophin</td>
<td>NGF</td>
</tr>
<tr>
<td>opioid</td>
<td>mu, delta, kappa, NOP</td>
<td>endorphine, enkephalin, dynorphin</td>
</tr>
</tbody>
</table>
Table 2. Examples of primary afferent and dorsal horn related receptors and ligands (adapted from “Acute pain management: scientific evidence, fourth edition” by Schug SA et al, The Medical Journal of Australia. 2016;204(8):315-7)

Immune mediators acting as signalling molecules in nociceptive pathways.
Legend: 5HT: serotonin; ASIC: acid-sensing ion channel; ATP: adenosine triphosphate; BK: bradykinin; NK1: neurokinin-1; P2X3: purinergic receptor subtype; PAR: proteinase-activated receptor; PGE2: prostaglandin E2; PGI2: prostacyclin; TRPV1: transient receptor potential. Others (e.g. H1, EP14, TRPV2) are designated subtypes of receptors rather than abbreviations; NOP: Nociceptin receptor also known as Orphanin FQ receptor (33).

There are two main types of axons which are the A-delta fibre axons and the C fibre axons (31). The A-delta fibre axons are myelinated and travel at a rate of 20 meters per second towards the central nervous system and the C fibre axons conduct at a slower pace of around two meters per second due to light or non-myelination of the axons (28). Hence, there are two phases of pain including an initial and immediate fast conducting phase by the A-delta fibre axons and a second delayed phase by the C fibre axons. The different phases translate to the experience of an initial sharp pain which is more localised followed by a dull ache which is less precise. (28).

A-delta and the C fibre axons synapse with secondary afferent neurons in the dorsal horn of the spinal cord (26). The dorsal horn has ten layers called the Rexed laminae, and this is also the site where there are complex interactions between excitatory and inhibitory interneurons and where descending inhibitory tracts from high centres exert their effects (26). The A-delta and C fibre axons transmit information to specific neurons mainly in the Rexed laminae I, II and V [34]. There are three main types of second-order neurons including nociceptive specific (responds to high-threshold noxious stimuli), wide dynamic range (responds to a range of sensory stimuli) and low threshold (responds to innocuous stimuli) (34).

Second-order neurons ascend to higher centres by the contralateral spinothalamic and spinoreticular tracts and subdivide into the lateral spinothalamic tract and the medial spinothalamic tract. (26). The lateral spinothalamic tract is also known as the ‘neospinothalamic tract’ and projects to the ventral posterolateral nucleus of the thalamus and then to the postcentral gyrus. The axons are somatotopically ordered and send collateral information to the midbrain and are involved in the sensory-discriminative aspect of pain. The medial spinothalamic tract which is also known as the ‘paleospinothalamic tract’ projects to the medial thalamus and affects the autonomic and affective component of pain (35). The spinoreticular tract is more phylogenetically ancient and projects to the hypothalamus by the nuclei of the brainstem reticular formation. The spinoreticular tract has little somatotopic organisation and is involved in the perception of diffuse pain and the emotional aspects of pain (26). Other known ascending spinal cord pathways include the spinomesencephalic, cervicothalamic and spinohypothalamic pathways. These pathways are also involved with the transmission of nociception and the autonomic and emotional aspects of pain (36).

The thalamus is involved in the processing of the somatosensory information from the ascending tracts (31). As described, the lateral and the medial spinothalamic tracts terminate in the respective nuclei and project to the primary and secondary somatosensory cortices, the insula, the anterior cingulate cortex and the prefrontal cortex which all have a role in processing nociception (26).

The descending tracts are pathways that have a central role in neuromodulation and descending inhibition (37). The brainstem, specifically the periaqueductal grey and the nucleus raphe magnus, are
involved in the inhibitory pathways. The periaqueductal grey is a region which surrounds the midbrain and receives input from the thalamus, hypothalamus, cortex and collaterals from the spinothalamic tract (37). The periaqueductal grey projects down to the nucleus raphe magnus which then have a direct effect on the dorsal horn cells and excitation of inhibitory neurons (37). The descending pathways activate through endogenous pathways related to serotonin and adrenaline, and a graphical representation is in Figure 2 (37).

Figure 2. The main ascending and descending spinal nociceptive pathways (adapted from “Acute pain management: scientific evidence, fourth edition” by Schug SA et al. The Medical Journal of Australia. 2016;204(8):315-7)

The main ascending and descending nociceptive pathways and the sites of action of some commonly utilised analgesic agents.

Legend: A: adrenergic nucleus; bc: brachium conjunctivum; cc: corpus callosum; Ce: central nucleus of the amygdala; DRG: dorsal root ganglion; Hip: hippocampus; ic: internal capsule; LC: Locus coeruleus; PAG: periaqueductal grey; PB: parabrachial area; Po: posterior group of thalamic nuclei; Py: pyramidal tract; RVM: rostroventromedial medulla; V: ventricle; VMH: ventral medial nucleus of the hypothalamus; VPL: ventral posterolateral nucleus of the thalamus; VPM: ventral posteromedial nucleus of the thalamus (33).

There is increasing evidence and interest in the perpetuating factors for the development of chronic pain without nociceptive stimuli including central sensitisation. (38). Central sensitisation occurs
through a complex interaction between neurotransmitters and the nociceptive pathways (39). Summation of repeated C fibre inputs results in a progressively more depolarised postsynaptic membrane and removal of the magnesium block from the N-methyl-D-aspartate (NMDA) receptor. Multiple neurotransmitters include glutamate and substance P and with progressive increases in stimuli; there is an increase in action potential output from the dorsal horn cell (40). This increase is termed ‘wind up’ and may lead to longer-term synaptic transmission called ‘long-term potentiation’. Both processes ultimately lead to central sensitisation which is characterised by upregulation and increased sensitivity of the nociceptive pathways (40). Central sensitisation is a decreased threshold for action potentials and spread beyond the area of tissue injury. The intracellular changes that occur in the process of central sensitisation include changes in the dorsal root ganglion and alterations in protein and gene expression. (38).

Unlike the nociceptive pathways and the somatosensory system; pain itself encompasses complex interactions with an individual’s psychology, experience and perception (41). Culture, beliefs, expectations, mood and the ability to cope influence pain. Psychological factors that affect the experience of pain includes processes of attention, cognitive processes, behavioural responses and interactions with the environment (41).

Attention is an active process in the pain experience, and pain may interrupt concentration through its intensity, catastrophic thinking, and the presence of emotional arousal (42). The role of learning processes is thought to be involved with conditioning and reinforcement of contingencies for pain. Empirical evidence supports the position of ‘fear of pain’ contributing to the development of avoidance responses to pain. (41). Negative appraisals of internal and external stimuli can contribute to the ‘fear of pain’, catastrophisation and behaviour changes (43). Catastrophisation is noted to be a significant factor in the development of chronic pain syndromes, and high levels of fear avoidance perpetuate the pain experience and poorer outcomes (44). Anxiety and depression have been found to contribute to the experience of pain. Studies show there are links between depression and anxiety and chronic pain states due to heightened arousal and its relation to psychological vulnerability and stress. (45). This understanding of pain and nociceptive pathways has implications for pain management and supports the holistic model. In particular, the distinction of nociception and pain is essential as it does not necessarily correlate with nociception (41).

1.1.4. Pharmacological Interventions for Chronic pain in Multiple Sclerosis

Pharmacological management is accepted and practised by clinicians and is essential in the management of pain in MS (46). Pharmacological management can range from opioids, anti-inflammatories to antineuropathic agents such as antidepressants and gabapentinoids and most recently cannabinoids as shown in Table 3 (16). There are recommendations and algorithms for chronic pain in MS mainly focusing on neuropathic pain and extrapolated from randomised controlled trials and systematic reviews (16, 46) However, limitations of pharmacological treatment include adverse effects, risk of dependence and addiction. Adverse effects can limit the achievement of a therapeutic dose, increase falls, leading to discontinuation of medications, polypharmacy and decreased satisfaction of treatment (47).

<table>
<thead>
<tr>
<th>Class</th>
<th>Action</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentinoids</td>
<td>Calcium channel blockade</td>
<td>Somnolence, dizziness, gastrointestinal symptoms,</td>
</tr>
<tr>
<td><strong>Opioids</strong></td>
<td>Central modulatory through central nervous system opioid receptors and peripheral opioid receptors on peripheral nerves</td>
<td>Constipation, sedation, pruritus, nausea, respiratory depression</td>
</tr>
<tr>
<td>-------------</td>
<td>-----------------------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Tricyclic antidepressants</strong></td>
<td>Alteration of central nervous system ratios noradrenaline, serotonin and or dopamine, sodium channel blockage</td>
<td>Sedation, balance problems, anticholinergic effects, impaired cognition, hypotension, weight gain, cardiac events</td>
</tr>
<tr>
<td><strong>Anti-inflammatory</strong></td>
<td>Decrease prostaglandins</td>
<td>Bronchospasm, gastrointestinal upset</td>
</tr>
<tr>
<td><strong>Noradrenaline and serotonin reuptake inhibitor</strong></td>
<td>Inhibits serotonin and noradrenaline uptake</td>
<td>Nausea, dry mouth, somnolence</td>
</tr>
<tr>
<td><strong>Antispasmodics</strong></td>
<td>Reduce impulse transmission from spinal cord to muscles</td>
<td>Dizziness, fatigue, respiratory failure</td>
</tr>
</tbody>
</table>


A list of medications used for pain in multiple sclerosis with the known mechanisms of actions and side effects (48).

1.1.5. Non-Pharmacological Interventions for Chronic pain in Multiple Sclerosis

Due to the limitations of pharmacological management; there has been increasing interest in non-pharmacological interventions for chronic pain in MS. (49). Non-pharmacological therapies are treatment modalities which are not drugs or medications (49). Given this broad definition; establishing what is effective is important to make recommendations in clinical practice and develop further research. Non-pharmacological interventions have mainly gained interest over the last few years due to relatively low-cost options, potential to help with other domains of pain and can use in conjunction with pharmacological interventions (50). However, non-pharmacological interventions remain underutilised mainly due to methodological difficulties with research and poor understanding of the mechanism of action. There are difficulties with awareness and attitudes towards non-pharmacological interventions but despite these inherent difficulties, there is still an interest in expanding the knowledge in this area (51). A list of common non-pharmacological interventions is listed in Table 4.

<table>
<thead>
<tr>
<th>Psychotherapies</th>
<th>Cognitive-behavioural therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypnosis</td>
<td></td>
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<tr>
<td>Biofeedback</td>
<td></td>
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<tr>
<td>Relaxation techniques</td>
<td></td>
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<tr>
<td>Family psychotherapy</td>
<td></td>
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<td>Group psychotherapy</td>
<td></td>
</tr>
<tr>
<td>Physical therapy</td>
<td>Exercise therapy</td>
</tr>
<tr>
<td>Transcutaneous electrical nerve stimulation</td>
<td></td>
</tr>
<tr>
<td>Occupational therapy</td>
<td></td>
</tr>
<tr>
<td>Acupuncture</td>
<td></td>
</tr>
<tr>
<td>Reflexology</td>
<td></td>
</tr>
</tbody>
</table>
Table 4. Common non-pharmacological interventions for pain in multiple sclerosis (adapted from “Chronic Pain Management: Nonpharmacologic Therapies” by Consultant 360 2013)

_A combination of physical and psychological therapies_ (52).

1.1.6. History of Pain in Multiple Sclerosis

MS was first differentiated and framed by Von Frerichs, Vulpian, Charcot and others around the world as a distinct disease in the 18th century (53). Further advances in the 21st century include an increased understanding of the pathophysiology of the condition, treatment options and community support groups (53). The understanding of pain in MS has also changed significantly over the years (6). Early published articles on pain in MS traces back to the 1950s and 1960s which reported a conservative prevalence figure of 13% (54). Carbamazepine was noted anecdotally to have some effect on facial pain, and possible pathophysiological mechanisms involved the substantia gelatinosa acting as a gate control mechanism (55). Demyelination was postulated to diminish the rate of conduction of the large unmyelinated fibres and increase the rate of fire of smaller fibres on the gate (56).

Headaches and facial pains were also discussed in the 1960s and recognised the link between trigeminal neuralgia and MS (57). Migraines in MS was noted to be common, and its pathophysiological mechanism was postulated to arise from an indirect effect on the autonomic system (58). In the 1980s the reported prevalence of pain was now said to be as high as 44% (59). Anecdotal treatment was mainly in the form of tricyclics and carbamazepine for paroxysmal pain symptoms. There were now descriptive studies that showed the significant impact of pain on sleep, work and relationships (60).

In the 1990s and 2000s, there was increasing literature on the prevalence of pain in MS in different settings such as residential facilities. However, there remained limited evidence for the management of pain, but there was now a greater awareness of a biopsychosocial model approach to pain (61). Further, there were increasing studies on the economic impact of pain in MS (6), systematic reviews on pharmacological (46) and non-pharmacological interventions (49), pathophysiology of pain in MS through animal studies (62) and medical imaging (63).

1.1.7. Pathophysiology of Chronic Pain in Multiple Sclerosis

Although chronic pain in MS is common, the underlying mechanisms are mostly unknown. The literature has primarily focused on animal studies which involve mice with experimental autoimmune encephalomyelitis (EAE) (64). Mice with EAE have been used to study MS-related complications and are known to exhibit chronic pain. These mice display hypernociception and allodynia in the form of reduced tail withdrawal to radiant heat and reduced pressure tolerance of the hindpaw (62).

EAE induction through central nervous system antigens correlates with surges of immune activation and changes in cytokine expression within the dorsal root ganglion (DRG). There is a peak expression of messenger ribonucleic acid (RNA) for tumour necrosis factor (TNF) alpha in the active EAE animal and the DRG (65). The pathogenic role of TNF alpha in chronic pain has been known to
induce neuropeptides involved with transduction of pain including substance P and calcitonin gene-related peptide (CGRP). TNF alpha has been shown to sensitise nociceptive neurons by induction of proinflammatory cytokine cascades and produce painful neuropathy when injected directly into the sciatic nerve (64). A review of the literature shows that neuropathic pain in MS is due to different mechanisms and a graphical representation shown in Figure 3 (65).

- Wnt proteins are involved in the development of chronic pain in MS. Wnt proteins are expressed in the central nervous system (CNS) and play an essential role in various processes of neural development including hippocampal formation, axonal remodelling, dendritic growth and synaptic differentiation and plasticity. Previous studies indicate a role of dysregulated Wnt signalling during the demyelination and remyelination in animal models (66).

- CNS demyelination induces sensory abnormalities as well as hind limb weakness and paralysis in EAE. These signs coincide with hyperexcitability of demyelinated axons, ectopic impulses, ephaptic activity and conduction blocks (65).

- Studies show a high prevalence of axonal damage in the CNS of EAE rodents due to direct damage from cytotoxic T cells and myelin autoantibodies. In humans with MS and mice with EAE; axonal damage occurs in active lesions in the white and grey matter. Axonal damage contributes to the ectopic firing of afferent sensory nerve fibres (65).

- Recruitment of T cells and innate immune cells play a part in the development of neuropathic pain in MS. Prophylactic administration of the immunosuppressant rapamycin to EAE mice attenuated the development of neuropathic pain through mechanisms associated with inhibition of effector T cells and glial cells. Other innate immune cells inhibited were mast cells, macrophages, neutrophils, dendritic cells and natural killer cells. (67).

- Proinflammatory cytokines, particularly interferon-gamma and interleukins, contribute to the disruption of the blood-brain barrier and induction of CNS neuroinflammation. Activated glial cells in the spinal cord release pro-inflammatory cytokines, glutamate and nitric oxide that amplify CNS hyperexcitability in neuropathic pain (68).

- In EAE mice neuropathic pain behaviours were abolished with the administration of glutamate transporter activator. Dysregulation of glutamate homeostasis can contribute to demyelination, axonal damage and neuropathic pain (69).

Studies have shown that demyelination of primary afferents at the trigeminal nerve root entry zone was present irrespective of MS or persistent neurovascular compression. Another hypothesis is that ephaptic spread secondary to juxtapositioning of demyelinated axons and cells within MS plaques can lead to a release of proinflammatory cytokines (70).
An overview of the pathophysiological mechanisms involved with chronic pain in multiple sclerosis. There are peripheral and central mechanisms involved with the perpetuation of chronic pain. These mechanisms include demyelination, interleukins, cytokines and T cells which contribute to hyperalgesia and dysregulation of pain.

Legend: CD: cluster of differentiation; TH: T-Helper; IFN: interferon; IL: interleukin; EAE: experimental autoimmune encephalomyelitis (65).

1.1.8. Imaging of Pain in Multiple Sclerosis

Previous literature has focused on establishing the association between the location of the demyelinating lesion and the site of pain. Recent research focuses on the implementation of additional imaging techniques including fluid-attenuated inversion recovery (FLAIR), diffusion tractography and incorporation of contrast enhancement (71).

Through advances in medical imaging; there has been the development of the ‘central vessel sign’ to detect migraines in MS as shown in Figure 4 [84]. In histopathological and imaging studies; a majority of MS plaques are around venous structures and identification of the ‘central vessel sign’ can be appreciated through 3T FLAIR (72). Co-registration of T2 FLAIR and postcontrast T2 weighted imaging showed higher cerebral vascular lesions in those with migraines and MS compared to those
without MS. Imaging has also demonstrated demyelinating lesions centred mainly around the structures of the substantia nigra and periaqueducral grey matter in those with migraines and MS (71).

In trigeminal neuralgia; conventional magnetic resonance imaging (MRI) has demonstrated demyelination in the trigeminal root entry zone, intrapontine tracts and trigeminal nuclei. These changes were reported as mainly bilateral and symmetrical (73).

Figure 4. Central vessel sign in multiple sclerosis (adapted from “Central vessel sign” on 3T FLAIR* MRI for the differentiation of multiple sclerosis from migraine”, by Solomon AJ, et al, Annals of Clinical and Translational Neurology. 2015;3(2):82-7)

There is growing experience in the use of imaging techniques in multiple sclerosis. The method of fluid attenuation inversion recovery imaging and 3D T2 images show perivenular lesions in the brain which are specific for multiple sclerosis and headaches (72).

1.1.9. Classification of Pain in Multiple Sclerosis

The International Classification of diseases 11th edition (ICD-11) is the most highly regarded classification system for chronic pain and will be discussed further in Chapter 3 (74). Specifically for chronic pain in MS; there are different types of pain which include trigeminal neuropathic pain, lhermitte's phenomenon, ongoing extremity pain, painful spasms, pain associated with optic neuritis, musculoskeletal pain, migraines and treatment-induced pains (12). This classification is a mechanistic approach and neuropathic, nociceptive and mixed qualities (12).

Ongoing extremity pain, trigeminal neuropathic pain and lhermitte's phenomenon are neuropathic types of pain owing to their pain descriptors, characteristics, post-mortem studies as well as imaging
studies. Pain associated with painful tonic spasms and spasticity are mixed pain type due to the dual mechanisms of hyperactivity in the central motor fibres and ischaemic pain. Finally, nociceptive pain can be musculoskeletal pain related to postural abnormalities and treatment-induced pains commonly associated with interferon treatment (11).

A different classification system based on cognitive behaviour classifies pain in MS into adaptive copers, dysfunctional and interpersonally distressed copers (75). Those classified as ‘interpersonally distressed’ were characterised by low levels of support from their partners and high psychological distress. ‘Adaptive copers’ show little interference with emotional distress or pain intensity while those classified in the ‘dysfunctional group’ have elevated levels of pain intensity, activity interference and emotional distress (75). This classification system could help with identifying those who are more likely not to respond to interventions and require greater health resources as well as tailoring interventions (75).

1.1.10. Measures of Pain in Multiple Sclerosis

Conventional measures of pain in MS include the pain visual analogue scale (VAS) and Numerical Rating Scale (NRS) as shown in Figure 5 (6). Other multidimensional pain measures included the brief pain inventory (BPI) and graded chronic pain scale and validated in chronic pain in multiple sclerosis (76).

Psychophysiological measures for chronic pain in MS may also be used such as quantitative sensory testing (QST) (77). QST measures of perception in response to control and allows for the evaluation and detection of pain thresholds. Domains tested in QST include temporal summation, spatial summation and descending control (77).

Testing for pain-related evoked potentials has been shown to be useful in the assessment of pain in MS. Pain-related evoked potentials is a neurophysiological method for assessing the functional component of nociceptive pathways. There are various methods used to evoke pain responses related to neuronal structures such as a laser, contact heat and potentials elicited by a concentric surface electrode (78).
Examples of common assessment tools and outcome measures for pain; the Visual Analogue Scale (VAS) and the Numerical Rating Scale (NRS). The NRS offers a linear form of assessment and involves rating ‘0’ to ‘10’ whereas the VAS offers a continuous aspect of measurement (79).

1.2. Overview of Transcranial Direct Stimulation

Transcranial direct stimulation (tDCS) is a non-invasive stimulation technique that can modulate cortical excitability as shown in Figure 6 (80). The use of tDCS is studied in multiple settings including cognition, depression, schizophrenia, upper limb function and pain (81, 82). Specifically for pain; there have been multiple meta-analyses showing a significant analgesic effect for neuropathic pain in spinal cord injury and fibromyalgia (82).
An example of transcranial direct stimulation (tDCS) set-up involving the anodal and cathodal electrodes and the primary device. The figure shows the anodal electrode placed over the ipsilateral dorsolateral prefrontal cortex, and the cathodal electrode positioned in the contralateral supraorbital area (83).

1.2.1. Mechanisms of Transcranial Direct Stimulation

The exact mechanism for tDCS for pain is not known, but there are multiple postulated mechanisms (84). The main site of action for tDCS is the primary motor cortex (M1) of the brain and stimulation of this area could relieve pain. Stimulation of M1 affects the regulation of the hypothalamic suppression network and the intervening cortical and subcortical synaptic connections. Other structures involved include the red nucleus, medial longitudinal fascicle and the thalamus (85).

There are three different types of stimulation possible with tDCS which includes anodal, cathodal and sham stimulation (82). Anodal stimulation augmenting neuronal excitability through positive stimulation, and cathodal stimulation decreases neuronal excitability through negative stimulation. Sham stimulation is used in a research setting for control. Effects can be sustained through long-term potentiation or depression and are related to modifying neuronal membrane polarity and its action potential generation threshold. Further discussion of its long-term effects will be in Chapter 6 (86).

The mechanism of tDCS involves direct current electrical fields which can affect cell migration through electrotaxis, differentiation and metabolism as shown in Figure 7 (83). Migration can be accounted for by localised shifts of intracellular calcium and the asymmetrical relocation of receptors within the membrane such as the acetylcholine and tropomyosin receptor kinase families (85). Other receptors affected include the N-Methyl-D-aspartic acid (NMDA) receptor through the removal of the magnesium plug and elevation of the brain-derived growth factor (84). Direct current electrical fields affect inflammatory responses including accelerating the migration of lymphocytes, monocytes, neutrophils, macrophages, polymorphonuclear cells and may also provoke quiescent microglial cells. There is data that supports angiogenesis of endothelial cells and leading to increased vascular endothelial growth factor, nitric oxide and interleukin (IL) 8 which all play a role in angiogenesis (87). In-vitro and in-vivo studies have shown anodal stimulation can increase neurite branches and decrease with cathodal stimulation (84).

Also, anodal tDCS has mu-opioidergic effects shown on positron emission tomography (PET) and mu-receptor selective radiotracer. The results showed a single active tDCS session decreased mu-opioid receptor binding potential in the subcortical areas including the nucleus accumbens, anterior cingulate cortex, insula and the posterior thalamus suggesting an analgesic effect through endogenous opioid release (88).
A schematic illustration of the proposed mechanisms of anodal transcranial direct stimulation (tDCS). Anodal tDCS is involved with hyperpolarisation of the membrane of the axon terminal. This hyperpolarisation consists of an increase in intracellular calcium, increased neurotransmitter release, depolarisation and long-term potentiation.

Legend: LTP: long-term potentiation; Na+: sodium; Ca++: calcium; K+: potassium; Mg++: magnesium; NMDAR: N-Methyl-D-aspartic acid receptor; AMDAR: α-amino-3-hydroxy-5-methyl-4-
isoxazolepropionic acid receptor; Cav: voltage-gated calcium channel; PSD: postsynaptic domain; TrK: tropomyosin-receptor kinase (84).

1.2.2. Evidence for Transcranial Direct Stimulation

Previous studies show tDCS used in different chronic pain syndromes such as neuropathic pain, phantom limb pain, complex regional pain syndrome (CRPS), chronic abdominal pain and non-neuropathic pain (82).

For chronic abdominal pain secondary to inflammatory bowel disease; anodal tDCS showed a reduction in pain scores greater than three months (89). A meta-analysis and systematic review of SCI and neuropathic pain was published in 2015. This review showed five studies had met the inclusion criteria which was needing a control group, have a spinal cord injury, greater than 18 years of age and pain for longer than three months. There was a pooled moderate effect for tDCS for reducing neuropathic pain severity in SCI (90).

Pain in fibromyalgia has been shown to be responsive to tDCS. A 2017 meta-analysis and systematic review showed there was a total of six randomised controlled trials (91). Results showed that anodal tDCS for fibromyalgia showed a pooled standardised mean difference (SMD) for the pain of -0.59 (91). For phantom limb pain, a double-blinded study showed a 28% reduction in pain relief using anodal tDCS, and this was sustained a week after treatment (92). In other conditions such as non-specific back pain; tDCS has been shown to be ineffective/ a double-blind randomised controlled study showed tDCS before cognitive behavioural therapy was ineffective compared to placebo for the reduction of pain and disability (93).

1.2.3. M1 Primary motor cortex in Transcranial Direct Stimulation

The M1 primary motor cortex is commonly involved in people with chronic pain and stimulation is characterised by increased cortical excitability and enhanced response (94). The M1 cortex is a key driver of motor output and is a contributor to movement dysfunction in pain (94).

Somatosensory changes associated with chronic pain have been noted in the literature and involved cortical, sensorimotor and neurochemical modifications (95). There are changes in M1 with cortico-cortical and cortico-spinal projections and low neurochemicals such as N-acetylaspartate (NAA) and myo-inositol (ml) (96). A low NAA level is associated with altered mitochondrial metabolism and change peripheral input in those with chronic pain (96).

Another study evaluated the anti-nociceptive effects of serotonin, noradrenaline and dopamine in M1 stimulation. This study showed attenuation of the M1 spinal antinociceptive effect by blocking the serotonergic innervation of the rostral ventromedial medulla (RVM) of rats (97). Another study showed the administration of a dopamine D2 antagonist reduced the excitability of the M1 cortex suggesting a dopaminergic role in neuromodulation. Stimulation of the M1 cortex activates locus core neurons and increased noradrenaline release with stimulation of descending inhibitory pathways (98).
1.3. Gaps in the Literature

Given the prevalence of chronic pain in MS, the significant impact on disability and its refractory nature there is a need for further research (6). Although the current literature is expansive, this thesis will build on and explore gaps in the existing knowledge base.

- There is a need for an updated summary of non-pharmacological interventions for chronic pain in MS despite a systematic review published in 2013 which included studies with low methodological qualities (49). Further work in this area would explore recent non-pharmacological interventions published and make recommendations based on high-level methodological studies.

- There is a lack of literature on longitudinal data for chronic pain in MS (8). The importance of exploring longitudinal relates to the persistent nature of chronic pain, and the progressive nature of MS. Longitudinal data is important to help with our current knowledge and prognostication of pain and its impact on individuals (9).

- There is little evidence to support the use of interdisciplinary management for chronic pain in MS. Multiple sclerosis poses a specific challenge with concerns regarding participation due to other coexisting impairments such as cognitive impairment, balance dysfunction and physical muscle weakness. However, it is these impairments which also point towards the benefits of interdisciplinary management from not only a pain severity perspective but also a functional perspective (99).

- Novel non-pharmacological interventions, such as neuromodulation, is an increasing area of interest due to a need for treatments which are safe and effective (51). There is limited evidence for neuromodulation in MS (82), and further studies are required.

1.4. Thesis Objective and Hypotheses

Aims of this thesis include:

- Summarising and analysing the current literature.
- Adding to the gaps in the literature.
- Making recommendations and conclusions.
- Improving knowledge in non-pharmacological interventions.
- Translation into clinical activity and practice to improve patient’s quality of life.

The hypotheses are that non-pharmacological interventions are:

- Safe and have minimal adverse effects.
- Effective in reducing pain severity.
- Effective in improving quality of life.
- Can be used in conjunction with current management for chronic pain in MS.

Reseaching in this area will help with further understanding of chronic pain in MS and help shape clinical practice and guidelines.
1.5. Thesis Structure

This thesis was organised into a logical and structured manner as represented in Figure 8. Study one is a systematic review of non-pharmacological interventions for chronic pain in MS. This systematic review will summarise recent literature following the ‘grades of recommendation, assessment, development and evaluation’ (GRADE) handbook (100). Study 2 will focus on expanding the knowledge on longitudinal data in an Australian cohort over ten years. This longitudinal study will explore prevalence, descriptors, pain-related disability and carers stress. Study 3 will evaluate the current practice of interdisciplinary pain management clinics for chronic pain in MS. Study 3 will be a retrospective study based on a recently developed database contributed by Australian and New Zealand pain clinics. This study will compare those have been to an interdisciplinary chronic pain clinic and have MS and central nervous system disorders and those who do not have these comorbidities. Study 4 will be a prospective randomised controlled trial comparing the effects of transcranial direct stimulation (tDCS) for chronic neuropathic pain in MS. This thesis will discuss and evaluate the overall findings in the previous chapters and conclude with recommendations for clinical practice, strengths and limitations, a summary of the findings and areas for future developments.
**Objective**
Assess the effectiveness of non-pharmacological interventions for chronic pain in MS.

**Introduction (Chapter 1)**
Narrative review of the literature to summarise and identify gaps in the literature. Overview of the thesis structure and hypothesis.

**Methodology (Chapter 2)**
Summary of overall methods of thesis

**Chapter 3**
Study 1 - Systematic review
Cochrane review on non-pharmacological interventions for chronic pain in MS
10 RCTs (N=580 participants)

**Chapter 4**
Study 2 - Descriptive and quantitative methods
10-year longitudinal study of chronic pain in MS. Study on pain characteristics, healthcare utilisation, quality of life, disability and carer stress
(N=744)
Analysed (N=73)

**Chapter 5**
Study 3 - Quantitative methods
Retrospective study on the effectiveness of interdisciplinary management for chronic pain in MS and CND. This study compared pain scores, self-efficacy, catastrophisation for those with MS and CND and those without
Total patients (N=40,672)

MS/CND (N=1924)
Completed outcomes (N=146)
Non MS/CND (N=38,748)
Completed outcomes (N=4281)
1.6. Summary of Chapter

Chronic pain in MS is common and has a significant impact on disability and quality of life. Studies have shown the prevalence of pain in MS ranging from 23% to 90% and longitudinal studies have shown that chronic pain is persistent up to 7 years (6). Classification of chronic pain in MS involves nociceptive, neuropathic, mixed and other chronic pain syndromes such as trigeminal neuropathic pain, lhermitte's phenomenon and painful tonic spasms (12). Chronic pain in MS has a significant impact at multiple levels including individuals and the community. There is difficulty with work, sleep, increased fatigue, lower physical activity and is consistently associated with significant mental health issues such as anxiety and depression. These issues all lead to a reduced quality of life (18).

Understanding the pain pathways is important, and there is a need for a distinction between nociception and pain. Nociception occurs when nociceptors detect noxious stimuli and pain is the result of higher brain processing and external influences (24). Nociception involves nociceptors in the peripheral tissues when then transmit to second-order neurons in the dorsal horn of the spinal cord; in the Rexed laminae. These pathways then travel through ascending tracts to the thalamus and the higher cortical centres for processing (26). Culture, beliefs, expectations, mood and the ability to cope influence pain. Psychological factors that influence the experience of pain includes processes of attention, cognitive processes, behavioural responses and interactions with the environment (41). Pharmacological interventions are the primary treatment modality for chronic pain in MS but have limited efficacy and risk of adverse effects. Common medications include opioids, anti inflammatories, antineuropathic agents such as antidepressants and gabapentinoids and cannabinoids (46). Although there have been developments; there remains a lack of literature on non-pharmacological interventions. This lack is due to methodological difficulties with research, poor
understanding of the mechanism of action and attitudes towards non-pharmacological interventions (49).

Chronic pain in MS is complex, and there are multiple proposed pathophysiological mechanisms for its persistent nature. Mechanisms proposed include Wnt proteins, CNS demyelination, axonal damage, cytotoxic T cells, proinflammatory cytokines and glutamate homeostasis (10). Overtime; there has been an improvement in using imaging, classification systems and measurements for chronic pain in MS. The use of 3T FLAIR and contrast enhancement has helped with the development of the ‘central vessel sign’. And measures of pain in MS include QST and pain-related evoked potentials (71).

TDCS for neuromodulation at M1 was studied in different chronic pain syndromes such as neuropathic pain, phantom limb pain, CRPS, chronic abdominal pain and non-neuropathic pain (82). The postulated mechanisms for tDCS include cell migration, NMDA activation, decreased inflammatory responses and mu-opioidergic effects (84). The M1 primary motor cortex is commonly involved in people with chronic pain, and tDCS caused increased cortical excitability and enhanced response to stimuli. Changes in M1 associated with chronic pain include changes in corticocortical and corticospinal projections and low NAA, ml, serotonin, noradrenaline and dopamine levels (94). There remain multiple gaps in the literature for chronic pain in MS. Specifically, an updated review of non-pharmacological interventions, longitudinal data for chronic pain in MS, the efficacy of interdisciplinary management and the use of novel non-pharmacological interventions.

The main aims of this thesis are to summarise and add to the current literature, make recommendations and improve knowledge to translate into clinical practice. The hypotheses are that non-pharmacological interventions are safe, effective in reducing pain severity, improve quality of life and can be used in conjunction with current management strategies. This thesis will be composed of four studies and will start with a systematic review on non-pharmacological interventions; followed by a 10-year longitudinal study on pain in the community, a retrospective study on the efficacy of interdisciplinary management and a randomised controlled trial using tDCS in neuropathic pain.

1.7. Conclusion

The introduction of this thesis highlights the significance of chronic pain in MS, the paucity of literature concerning non-pharmacological interventions and the need for further developments in this area. The next chapter will focus on the methodology of the overall thesis including framework, methods, settings, data collection and procedures.
Chapter 2. Methodology

2.1. Introduction

This chapter describes the overall methodology used for the four studies in this thesis. The methods for Studies 1, 2, 3 and 4 are summarised in Section 2.2 and a more detailed description of methods in each of their respective chapter. The other sections of this chapter will include

- Procedures for ethics application
- The recruitment of study subjects
- Methodological challenges
- Outcomes of the objections

The design of this thesis was chosen due to develop research required in the field of non-pharmacological interventions for chronic pain in MS.

2.2. Ethics

The Melbourne Health HREC, following the National Statement on Ethical Conduct in Human Research 2007, approved the studies in this thesis. If applicable, each participant received an information sheet and consent form is written in plain English which they signed after a verbal explanation of the project from the primary investigator and a further opportunity to ask questions was offered. Research data sheets were kept confidentially and locked in a recruitment centre, and coded information was entered and kept in a password-protected database and computer system.

2.3. Population

The study population included participants with MS and included other central nervous system disorders such as Parkinson's disease, spinal cord injury, strokes and acquired brain injuries if a greater sample size was required. Patients were excluded if they were medically unwell, unable to communicate due to severe language impairment or lost to follow up.

2.4. Assessment procedures

Recruitment and assessments were undertaken between February 2016 and June 2018. Recruitment occurred through a variety of sources including the community-based in Melbourne and MS patients known to the Royal Melbourne Hospital. These patients were either known to the chronic pain clinic, rehabilitation clinic or inpatient rehabilitation patients. Structured baseline and outcome assessments were done where applicable, and further details of assessments are found in the methods section of Study 1, 2, 3 and 4. Contact with patients was face-to-face with the assessor. The assessor was also
involved in recording initial and outcome assessments where applicable. Follow-up differed according to the study but did not extend greater than a month after treatment. The follow-up period was selected to detect short-term changes and other logistical reasons such as feasibility, resources and funding.

2.5. Data Collection and Analyses
Each study required its methods for data collection and analysis. Statistical significance was taken as a p-value of >0.05, and this thesis used statistical package for social sciences (SPSS) version 23 for statistical analysis. Data was collected and analysed from different sources including literature reviews, observational data, interviews, clinical databases and prospective clinical data. The collection of data was done concurrently to save time and for greater efficiency. The majority of data was entered into Microsoft Excel and later imported into SPSS format and protected by a password.

2.6. Procedures
Mixed methods, with quantitative and descriptive methods, were mainly used for this thesis. Quantitative methods were used to quantify the problem through numerical data and statistics. Types of studies in this thesis include; a systematic review, retrospective study, longitudinal observational study and prospective randomised controlled trial. The variation in data collection leads to greater validity when a single methodology does not provide all the information. The frameworks and planning of the thesis involved methods which would expand the current knowledge on non-pharmacological interventions for chronic pain MS. Each chapter was submitted to a peer-reviewed medical journal and reviewed by experts in this area.

2.7. Rationale for Methods and Frameworks
This thesis and each study were based on methodological models, frameworks and guidelines suggested by the current literature. Quantitative and descriptive methods were used to investigate and evaluate the components of this thesis and address the following:

- What was the intervention?
- Does the intervention work?
- Was it implemented as planned?
- What were the outcome measures?
- What were the strengths and limitations?
- What were the implications to clinical practice?

The following methodological models and frameworks helped develop and support this thesis.

- International Classification of Diseases 11th Revision (ICD-11) (74)
- A Taxonomy for Disease Management from the American Heart association Disease Management Taxonomy Writing Group (101)
- Consolidated Standards of Reporting Trials (CONSORT) (102)
2.7.1. Classification of Chronic Pain for International Classification of Diseases 11th Revision

The ICD-11 is a taxonomy for chronic pain and provides a conceptual framework for the classification and coding of chronic pain syndromes as represented in Figure 9. The ICD-11 is commonly used in research and is a pragmatic framework for multi-layered classification involving etiology, pathophysiology and body site (74). The ICD-11 is divided into seven groups including:

- Chronic primary pain: Pain in one or more anatomic regions that persists or recurs for longer than three months and is associated with significant emotional distress or significant functional disability.
- Chronic cancer pain: Pain caused by the cancer itself and the pain caused by the cancer treatment.
- Chronic post-traumatic and post-surgical pain: Pain develops after a surgical procedure or a tissue injury at least three months after surgery or tissue trauma
- Chronic neuropathic pain: Pain caused by a lesion or disease of the somatosensory nervous system.
- Chronic headache and orofacial pain: Headaches and orofacial that occur on at least 50% of the days during at least three months.
- Chronic visceral pain: Recurrent pain that originates from the internal organs.
- Chronic musculoskeletal pain: Persistent pain or recurrent pain that arises as part of a disease process affecting bone, joint, muscle or related soft tissue (74).

The ICD-11 was developed by the World Health Organisation (WHO) and International Association for the Study of Pain (IASP) task force which are international bodies with significant stakeholders and influence on pain policies. Chronic pain was defined as persistent or recurrent pain lasting longer than three months so that it is clear and operationalised (74).

Although not all the listed classifications of ICD-11 may be relevant to chronic pain in MS; there are still categories which are significant. As described in Chapter 1, chronic primary, neuropathic, headaches, orofacial, visceral and musculoskeletal pain are common pain syndromes in MS (6). Therefore, this taxonomy framework is important for this thesis because it ensures the use of a common, standardised and consistent language. This taxonomy is supported by well-recognised bodies and recognises the diagnostic entity of chronic pain and a broad range of syndromes experienced by those with MS (74). This taxonomy system was incorporated in Studies 1 to 4.
2.7.2. A Taxonomy for Chronic Disease Management

The Taxonomy for Disease Management from the American Heart Association Disease Management Taxonomy Writing Group provides a conceptual framework for chronic disease management (101). The Disease Management Taxonomy is comprehensive and can be applied to chronic pain in MS as a disease entity. The Disease Management Taxonomy is composed of eight domains which were incorporated in the evaluation and the development of Studies 1 to 4. The domains include:

- Patient population: Characterised by risk status, demographic profile and level of comorbidity.
- Intervention recipient: Describes the primary targets of disease management intervention and includes patients and caregivers, physicians and allied healthcare providers and healthcare delivery systems.
- Intervention content: Delineates individual components such as patient education, medication management, peer support, or some form of post-acute care, that are included in disease management.
- Delivery personnel: Describes the network of healthcare providers involved in the delivery of disease management interventions, including nurses, case managers, physicians, pharmacists, case workers, dieticians, physical therapists, psychologists and information systems specialists.
Method of communication: Identifies a broad range of disease management delivery systems that may include in-person visitation, audio-visual information packets, and some form of electronic or telecommunication technology.

Intensity and Complexity: Distinguish between frequency and duration of exposure as well as the mix of program components, concerning the target for disease management.

Environment: Defines the context in which disease management interventions are typically delivered and includes inpatient or hospital-affiliated outpatient programs, community or home-based programs, or some combination of these factors.

Clinical outcomes: Include traditional, frequently assessed primary and secondary outcomes, as well as patient-centred measures, such as adherence to medication, self-management and caregiver burden (101).

These domains were relevant to this thesis as it provided a backbone to the evaluation of chronic pain in MS. This framework was especially important in reviewing the current literature and assisting in the development of future guidelines and service delivery. Each study aims to address each of the domains including defining the patient population, the intervention, environment and clinical outcomes. This is especially true in Study 3 which focused on an interdisciplinary pain management program and will be discussed further in Chapter 5.

2.7.3. Consolidated Standards of Reporting Trials 2010

The CONSORT statement is a framework and guideline intended to help improve the reporting, interpretation, assessment and design of a randomised controlled trial (107). This statement was developed through collaboration and consensus between experts in this area including methodologists, guideline developers, knowledge transition specialists, and journal editors. The CONSORT statement comprises of a 25-item checklist and the broad categories assessed include (102):

- Title and abstract
- Introduction
- Methods
- Results
- Discussion
- Other information

The Consort statement is widely used and endorsed by medical journals and has been shown to improve reporting of randomised trials (102). This framework has been particularly important in this thesis for the development of the randomised controlled trial in Study 4. Study 4 implemented the following headings and flow diagrams as to standardise formatting and be transparent in its limitations which is important for future reviewers.
2.7.4. Initiative on Methods, Measurement and Pain Assessment in Clinical trials

Research in the area of chronic pain can be difficult due to short-term follow-up and variability in outcome measures (103). The IMMPACT recommendations were published in 2003 and is a consensus document from experts in the area of research (103). Stakeholders included participants with backgrounds in academia, governmental agencies, a self-help organisation and the pharmaceutical industry (108). To ensure the outcome measures selected were of high quality; they were evaluated with the following domains:

- Appropriateness of the measures content and conceptual model
- Reliability
- Validity
- Responsiveness
- Interpretability
- Precision of scores
- Respondent and administrator burden and acceptability
- Respondent and administrator burden and feasibility
- Availability and equivalence of alternate forms and methods of administration
- Availability and equivalence of versions for different cultures and languages (108).

The IMMPACT recommended core outcome measures include pain, physical function, emotional function, participant ratings of global improvement and satisfaction with treatment and symptoms and adverse events. A summary of the outcome measures are is represented in Table 5 (108).

Pain Intensity: Common measures for pain intensity include the visual analogue scale (VAS), numerical rating scale (NRS) and the verbal rating scales (VRS) which are reliable and no scale has demonstrated greater responsiveness in detecting improvements with pain management. It is recommended that the percentages of patients obtaining reductions in pain intensity of at least 30% should be reported and if possible at least a 50% reduction is ideal.

Rescue analgesia and joint pain treatments: The use of rescue medications and other pain-related treatments should be assessed. The use of rescue medications can be used as an outcome measure in clinical trials and can provide additional measures of efficacy.

Pain quality and temporal aspects of pain: Measures of the affective and sensory qualities of pain may help with identifying the efficacy of treatments for certain aspects of pain. Whereas, pain intensity reflects the overall magnitude of the pain; pain affect reflects the distress caused by the pain. A common outcome measure for pain quality is the Short Form McGill Pain Questionnaire (SF-MPQ). Temporal aspects of pain should also be considered including variability in intensity, time to onset for meaningful pain relief, the durability of pain relief and frequency, duration and intensity of pain.

Physical functioning: Many studies have demonstrated that pain intensity and physical functioning are associated and this supports the importance of measuring physical function in chronic pain clinical trials. Examples of physical functioning measures include Multidimensional Pain Inventory (MPI), Brief Pain Inventory (BPI) and the Short Form - 36 Health Survey.
Emotional Functioning: Chronic pain is commonly accompanied by symptoms of psychological distress and psychiatric distress. Recommended outcome measures suggested by IMMPACT consensus meeting include the Beck Depression Inventory (BDI) and the Profile of Mood States (POMS). The assessment of emotional functioning in chronic pain is difficult due to the similarities of symptoms with medications but have been validated and responsive when used in the medically ill.

Participant Ratings of Global Improvement and Satisfaction with Treatment: Global ratings of improvement and satisfaction provide an opportunity for participants to aggregate their experience with the trial in one outcome measure. The recommended outcome measure is the Patient Global Impression of Change Scale (PGIC) which provides a responsive and readily interpretable measure of the participant’s assessments of the course of the clinical trial.

Participant disposition: The IMMPACT consensus meeting recommended the collection of participant disposition including recruitment of participants, progression through the trial, doses and duration of treatment and the extent to which the participant adhered to the protocol. Collection of patient disposition is important for the validity and feasibility of the clinical trial (108).

These domains and core outcome measures should be considered when designing clinical trials for chronic pain treatments (108). This thesis has used the recommended IMMPACT outcome measures during the design of the studies, and these recommendations highlight the complex and multidimensional nature of chronic pain. However, there were limitations with using the IMMPACT framework mainly regarding:

- Not all outcome measures were relevant to the study
- Other outcomes measures were included in the study were more specific for MS pain
- Due to feasibility; not all outcome measures were included

Regardless, the inclusion of the IMMPACT framework to standardised outcome measures and improve the validity and clinical applicability of the clinical trials in this thesis.

<table>
<thead>
<tr>
<th>Table 5. Standardised outcome measures of IMMPACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
</tr>
<tr>
<td>11-point (0–10) numerical rating scale of pain intensity</td>
</tr>
<tr>
<td>Usage of rescue analgesics</td>
</tr>
<tr>
<td>Categorical rating of pain intensity (none, mild, moderate, severe) in circumstances in which numerical ratings may be problematic</td>
</tr>
<tr>
<td>Physical functioning (either one of two measures)</td>
</tr>
<tr>
<td>Multidimensional Pain Inventory interference scale</td>
</tr>
<tr>
<td>Brief Pain Inventory interference items</td>
</tr>
<tr>
<td>Emotional functioning (at least one of two measures)</td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
</tr>
<tr>
<td>Profile of Mood States</td>
</tr>
<tr>
<td>Participant ratings of global improvement and satisfaction with treatment</td>
</tr>
<tr>
<td>Patient Global Impression of Change</td>
</tr>
<tr>
<td>Symptoms and adverse events</td>
</tr>
<tr>
<td>Passive capture of spontaneously reported adverse events and symptoms and use of open-ended prompts</td>
</tr>
<tr>
<td>Participant disposition</td>
</tr>
<tr>
<td>Detailed information regarding participant recruitment and progress through the trial, including all information specified in the CONSORT guidelines</td>
</tr>
</tbody>
</table>
Recommended outcome measures for clinical trials of chronic pain treatment efficacy and effectiveness (108).

2.7.5. International Classification for Functioning

The ICF is a classification of health and health-related domains and occurs in the context of individual and environmental factors as shown in Figure 10 (109). The broad categories and components of this framework include:

- Body functions and structure
- Activities (related to tasks and actions by an individual) and participation (involvement in a life situation)
- Additional information on severity and environmental factors (110)

ICF views functioning and disability as dynamic and placing the model as a measure of function rather than the condition. The ICF lends itself nicely for the development of chronic pain models by providing a ‘workable’ visual profile for functioning and disability (104). The concepts related to chronic pain are similar and relate to the ICF classification system due to its multidimensional nature. All aspects of a patient's life are incorporated into the ICF to focus on patient function and disability (104).

![Figure 10. Components of ICF](image)

A diagram of the interactions between the components of International Classification of Function (ICF) (111).

In this thesis, each of the studies was based on the ICF framework for outcome measures and designing trials. The use of outcome measures favouring function is also favoured by the IMMPACT framework (111). The ICF classification is useful to classify patient functioning and body functions, structures, activities and participation (104). These are contextual factors that influence the delivery of rehabilitation and pain programs which is a focus and discussed in Study 3.
2.7.6. Australian Health Outcomes Collaboration

The AHOC is based in the University of Wollongong and houses several national consortia and collaboratives (105). AHOC is involved in research and implementation of health outcomes, measurement and benchmarking tools. Other health initiatives from the University of Wollongong include ePPOC which is an electronic database containing data from Australian and New Zealand pain clinics and is discussed further in Study 3. The AHOC was derived from a number of issues (105):

- An increasing proportion of expenditures going to the health care and/or the need for cost containment
- The recognition of the serious limitations of available information about the effects of many services and treatments
- The percentage of large hospital variations in the use of medical procedures between geographical areas and between physicians.
- Concerns as to whether new technologies are improving patient’s well-being.
- Concerns about the quality of care.
- The increasing empowerment of consumers/patients (105).

Given the increasing issues in healthcare; there is a need for a framework to define performance and offer standardised measurements and evaluation tools (105). This thesis has incorporated these concerns into its development and discussion of integration into clinical practice. The studies associated with this thesis had focused on researching new treatments, quality of care and recognising the limitations and effectiveness of current healthcare practices.

2.7.7. Medical Research Council Framework

Process evaluation is essential for designing and testing complex interventions and the MRC framework was published to help researchers adopt appropriate methods (106). Complex interventions are defined as interventions that comprise of multiple interacting components. The MRC framework for the development of complex interventions and has been used successfully across different disciplines (106). Complex interventions in this thesis include an interdisciplinary program for pain management and tDCS for neuropathic pain in MS which have multiple dimensions and interacting components of complexity.

The original MRC framework focused on the development and evaluation of randomised controlled trials (RCT) which are regarded as the highest form of casual evidence. However, robust methodology may not be feasible in all research areas including pain management in MS (6). The new MRC guidelines published in 2006 extended the coverage to non-experimental methods, such as observational studies, to help researchers choose the appropriate methods (106). Where possible this
thesis had considered a RCT design; but due to feasibility, applicability to a large organisation, service delivery and intervention and participation constraints this was not always possible. Challenges relating to the methodology of this thesis for chronic pain in MS include:

- Difficulty with blinding in methods due to limited staffing, funding and the nature of non-pharmacological management.
- Prospective trial not possible due to difficulty with implementation, lack of pilot trials and limited staffing.
- RCT not the appropriate method for objectives of thesis including prevalence, reviews and development of new frameworks.
- Difficulty with recruitment and numbers required for statistical significance.

Key steps of developing this thesis include feasibility and piloting, development, implementation and evaluation as shown in Figure 11. The updated MRC guidelines for the evaluation of complex interventions emphasise the importance of a detailed description of each of these domains to which this thesis implements.

![Figure 11. Implementation of thesis through MRC framework](image)

An outline of this thesis implementation adapted from the Medical Research Council Framework. Studies 1 and 2 have been used for the development of this thesis and Studies 3 and 4 are pilot studies with evaluation and elements of implementation (106).

### 2.8. Outcome Evaluation

Outcome evaluation comprised of mixed methods. A quantitative approach and descriptive methods were used to assess program effectiveness. Primary and secondary outcome measures were selected from well-planned frameworks and guidelines such as AHOC and IMMPACT. Outcome measures were selected based on validity, ease of application and specificity for the aims and objectives of the study. The primary and secondary outcomes used in the studies of this thesis include:

- Brief Pain Inventory (BPI)
- Chronic Pain Grade (CPG)
- Carer Strain Index (CSI)
● Depression Stress Anxiety Scale (DASS)
● Multiple Sclerosis Quality of Life (MSQOL 54)
● Patient Catastrophizing Scale (PCS)
● Patient Self Efficacy Questionnaire (PSEQ)
● Visual Analogue Scale (VAS)
● Neuropathic Pain Scale (NPS)
● Short Form McGill Pain Questionnaire (SFMPQ)

Further details and the rationalisation of choosing each of the outcome measures is detailed under methods in Chapters 3 to 6.

2.9. Summary of Chapter

This thesis was completed by mixed methods and ethics was obtained from the Melbourne Health HREC, following the National Statement on Ethical Conduct in Human Research 2007. If applicable, each participant received an information sheet and consent form written in plain English which they signed after a verbal explanation of the project. Research data sheets were kept confidentially and locked in a recruitment centre, and coded information was entered and kept in a password-protected database and computer system.

The study population included participants with MS and other central nervous system disorders such as Parkinson's disease, spinal cord injury, strokes and acquired brain injuries if a greater sample size was required. Participants were recruited from Melbourne and known to the Royal Melbourne Hospital or from a clinical pain database. Participants were excluded if they were medically unwell, unable to communicate due to severe language impairment or lost to follow-up.

Structured baseline and outcome assessments were done where applicable, and follow-up differed according to the study but did not extend greater than a month after treatment. Each study required its methods for data collection and analysis. Statistical significance was taken as a p-value of >0.05 and this thesis used SPSS version 23 for statistical analysis. Mixed methods were mainly used for this thesis. Quantitative methods were used to quantify the problem through numerical data and statistics. Types of studies in this thesis include; a systematic review, retrospective study, longitudinal observational study and prospective randomised controlled trial.

This thesis and each study were based on methodological models, frameworks and guidelines suggested by the current literature. The following methodological models and frameworks helped develop and support this thesis including ICD-11 (74), A Taxonomy for Disease Management from the American Heart Association Disease Management Taxonomy Writing Group (101), CONSORT (102), IMMPACT (103), ICF (111), AHOC (105) and MRC framework (105). Outcome evaluation comprised of mixed methods. A quantitative approach and descriptive methods were used to assess program effectiveness.
2.10. Conclusion

Due to the broad topic of non-pharmacological interventions for chronic pain in MS, this thesis used different methods for each study. There were many methodological considerations for the studies involved in this thesis including ethics, patient populations, intervention considerations, statistical analyses and outcome measures. In addition to this, frameworks and guidelines which were developed by expert groups were used in the development of the thesis. The next chapter will present the first study which is a systematic review on the non-pharmacological management of chronic pain in MS.
Chapter 3. Non-pharmacological Management of Chronic Pain in Multiple Sclerosis

3.1. Introduction

Given that we know the significance of chronic pain in MS, its impact on individuals and the methodological considerations in Chapter 2; a systematic review of the most current literature is important for this thesis. Hence, this chapter will outline the background, methods, results and discussion of the systematic review.

In general, pain in MS is treated with pharmacological agents (112-115) and non-pharmacological modalities or a combination of both (116). 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 (117, 118). A wide range of non-pharmacological interventions has been trialled for the management of pain in MS. Previous studies (117-120) have found that MS patients in the community setting frequently use a wide variety of non-pharmacological techniques, which 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 (9, 120). 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.

3.1.1. 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 peripheral pathways, CNS lesions causing hyperexcitability, and increased neuronal (nerve cell) activity at the site of the lesion in the spinal cord (121-124). Chronic pain may 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 or a non-noxious stimulus or can also occur spontaneously in the absence of any definable trigger (122, 125, 126). Due to this heterogeneity of chronic pain aetiology amongst people with MS, modalities that act at different sites along the pain processing pathway may have variable degrees of effectiveness (75, 124).

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 (127), 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 with pain (128). 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 behaviour and mood.
3.1.2. Why It Is Important To Do This Review

Pain is prevalent in people with MS and tends to increase over time, due to the disease process itself and from MS-related complications, and is associated with a great interference with people with MS’ daily life activities (9). Several studies have demonstrated that those with higher pain grades reported more disability and healthcare visits, and lower quality of life (QoL) (120). Non-pharmacological therapies are widely used, both in hospital and ambulatory/mobility settings, to improve pain control, coping ability, daily function and QoL in people with MS. Chronic pain is found to be amenable to multidisciplinary rehabilitation management (116, 129-132). Psychological interventions have shown potential beneficial impact on people with MS, including the management of symptoms such as pain and fatigue (133). Further, TENS is commonly trialled for chronic low back pain in people with MS and hypoalgesic effects (134). Similarly, anodal tDCS has demonstrated effectiveness in reducing central chronic pain in the MS population (135). To our knowledge, there is only one published systematic review on non-pharmacological management in people with MS (49), which excluded non-spastic and non-trigeminal pain. This review identified the main categories of non-pharmacological interventions, which included education, electrical and physical therapy. The reviewers found that low-frequency TENS had the greatest reduction in pain scores (49). This systematic review did have several limitations, including inclusion of non-randomised clinical trials and pilot studies, and exclusion of various non-pharmacological interventions, such as acupuncture, massage therapy, thermotherapy, electrical therapy such as transmagnetic stimulation (TMS) and tDCS. An updated systematic evaluation of the existing evidence is therefore needed to determine the effectiveness and safety of all non-pharmacological modalities to provide treating clinicians clear guidance for clinical decision-making for appropriate pain management in people with MS.

3.2. Objectives

This review aimed to investigate the effectiveness and safety of non-pharmacological therapies for the management of chronic pain in people with MS. Specific questions to be addressed by this review include the following.

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

3.3. Methods

This section will discuss the criteria for considering studies for this review.

3.3.1. Types of Studies

All published randomised controlled trials (RCTs), including cross-over studies that compared non-pharmacological interventions with no treatment, sham and usual care, for managing chronic pain in people with MS were included. Clinical controlled trials (CCTs) were eligible for inclusion, but none were identified. We included only trials with a full journal publication, 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 excluded studies of experimental pain, observational studies, case reports, and clinical observations.

3.3.2. Types of Participants
We included trials if the study population had a confirmed diagnosis of MS based on standard criteria [154] and participants were aged 18 years and older with chronic pain. All studies with participants with 'chronic pain' or participants suffering from pain longer than three months were included, irrespective of the use of varying definitions for chronicity of pain. We included studies that recruited participants with the minimum levels of pain on visual analogue scale (VAS) of 3/10. Studies including participants with other diagnoses were excluded unless individual data for the people with MS could be obtained either from the published results or through contact with authors.

3.3.3. Types of Interventions
All non-pharmacological interventions to manage chronic pain in people with MS delivered in any settings (inpatient, outpatient, community, or home-based) were included.

- 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, defined as any co-ordinated 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 chronic pain.

Control interventions that are likely used for comparison with the above mentioned interventions include no treatment, sham and usual care.

3.3.4. Types of Outcome Measures
Diverse outcomes were expected, given the varied presentations of pain-related problems and goals of treatment related to pain severity in MS.

3.3.4.1. Primary Outcomes
The primary outcome determined whether the intervention produces reduction in pain measured by validated measures, such as a visual analogue scale (VAS) or numerical rating scale (NRS) (136), Likert scale such as the Patient’s Global Impression of Change (PGIC, (137)), or Clinical Global Impression of Change (CGIC, (138)), or specific pain scales such as the McGill Pain Questionnaire (MPQ, (139)), Short Form McGill Pain Questionnaire (SFMPQ, [159]), or Brief Pain Inventory (BPI, (140)), and others (subjective or objective). We used the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) (141) criteria, defined as:

- at least 30% pain relief over baseline (moderate);
- at least 50% pain relief over baseline (substantial);
- much improved on Patient Global Impression of Change Scale (PGIC; moderate);
- very much improved on PGIC (substantial).
3.3.4.2. Secondary Outcomes
Due to the multidimensional model of pain, we included secondary outcomes determining whether the change in pain by the intervention affects the other specific outcome(s) measured by validated tools, which included:

- other symptoms or impairments, such as spasticity, fatigue, e.g. Multiple Sclerosis Spasticity Scale (MSSS-88, (142)); Modified Ashworth Scale (MAS, (143)); Fatigue Impacts Scale (FIS, (144)); Modified Fatigue Impact Scale (MFIS, (145)); Fatigue Severity Score (FSS, (146));
- functional activity, e.g. Functional Independence Measure (FIM, (147)); Barthel index (BI, (148)); Rowland Morris Disability Questionnaire (RMDQ, (149));
- psychosocial outcomes, e.g. Beck Depression Inventory (BDI, (150)); Depression, Stress and Anxiety Scale (DASS, (151)); Hospital Anxiety Depression Scale (HADS, (152)); Patient Health Questionnaire 9 (PHQ-9, (153));
- restriction in participation/impact on carers, e.g. Caregiver Strain Index (CSI, (154));
- vocational outcomes, e.g. Work Instability Scale (WIS, (155));
- quality of life, e.g. Multiple Sclerosis Quality of Life (MSQOL54, (156)); Short Form Health Survey (SF-36, (157)); Leeds Multiple Sclerosis Quality of Life (LMSQOL, (158)); Multiple Sclerosis Impact Scale (MSIS-29, (159));
- withdrawals, due to lack of efficacy;
- outcomes that reflect utilisation of healthcare 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, that may jeopardise the person or may require intervention

3.3.5. Timing of Outcome Measures
We divided outcome time points into short term (up to three months) and long term (greater than three months) from the start of the intervention.

3.3.6. Search Methods for Identification of Studies
We considered articles in all languages with a view to translation, if necessary.

3.3.7. Electronic Searches
The Information Specialist searched (up to 10 December 2017) the Trials Register of the Cochrane MS and Rare Diseases of the CNS Group, which, among other sources, contains trials from:

- Cochrane Central Register of Controlled Trials (CENTRAL) (2017, issue 12);
- MEDLINE (PubMed) (1966 to 10 December 2017);
- Embase (Embase.com) (1974 to 10 December 2017);
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCOhost) (1981 to 10 December 2017);
• Latin American and Caribbean Health Science Information Database (LILACS) (Bireme) (1982 to 10 December 2017);
• ClinicalTrials.gov (https://clinicaltrials.gov/); and
• World Health Organization (WHO) International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/).

The keywords that were used to search for trials for this review. 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 MS and Rare Diseases of the Central Nervous System Group's module.

In addition we searched the following databases:

• PsycINFO (1980 to 10 December 2017);
• Allied and Complementary Medicine Database (AMED) (1985 to 10 December 2017); and
• MANTIS/Ovid (for most recent data available).

3.3.8. Searching Other Resources

We conducted an expanded search to identify articles potentially missed through the database searches and articles from ‘grey literature’. These were:

• 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.

3.3.9. Selection of Studies

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

3.3.10. Data Extraction and Management

Two review authors (BA, JY) independently extracted the data from the included trials using a standardised form and entered the data into the RevMan software (160), which included:

• 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 was made by a third review author (FK). To summarise all data on reduction in pain, we used the benchmarks of the IMMPACT recommendations for the evaluation of reduction in pain [121]. We summarised all studies that met the inclusion criteria in the Characteristics of included studies table (Table 7).

3.3.11. Assessment of Risk of Bias in Included Studies

Two review authors (BA, JY) independently assessed the methodological quality of the included studies using the 'Risk of bias' tool outlined in the Cochrane Handbook for Systematic Reviews of Interventions (161). We assessed the following for each study:

- **Random sequence generation** (selection bias): we assessed 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 excluded studies with a non-random process.
- **Allocation concealment** (selection bias): we assessed 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 assessed 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).
- **Blinding of participants and personnel** (performance bias): we assessed the methods used to blind study participants, personnel. We assessed methods as low risk of bias (study states it was blinded and described the method used to achieve the blinding) and unclear risk of bias (study stated it was blinded but did not provide adequate description of how this was achieved).
- **Blinding of outcome assessment** (detection bias): we assessed the methods used to blind the allocated interventions by outcome assessors. We assessed methods as low risk of bias (study states blinding of outcome assessments ensured) or unclear risk of bias (when method is not clearly stated) and high risk (no blinding of outcome assessment)
- **Incomplete outcome data** (attrition bias): we assessed 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).
- **Selective reporting** (reporting bias): we assessed the methods used to report outcomes and selective reporting. We assessed methods as low risk of bias (all of the study’s prespecified
outcomes and protocol is available), unclear risk (insufficient information) or high risk (not all of the study's prespecified outcomes is reported).

- Other bias: we assessed other bias as low risk (free of other sources of bias), unclear risk (insufficient information) or high risk (potential source of bias).

Any disagreements or lack of consensus was resolved by the third review author (FK).

### 3.3.12. Measures of Treatment Effect

All quantitative data were entered and analysed in the RevMan software (160). For each outcome of interest, summary estimates of treatment effect (with 95% confidence intervals (CIs)) for each comparison were calculated. Where possible, risk ratios (RRs) with 95% CIs for dichotomous data and difference in means or standardised difference in means (SMD) with 95% CIs for continuous data were calculated. The results of individual studies were discussed and presented in table and graphical format, where data aggregation was not possible.

### 3.3.13. Unit of Analysis Issues

The appropriate unit of analysis involved the type, intensity, and setting of non-pharmacological interventions. A qualitative analysis using the GRADE approach for existing evidence was attempted in any event (161). Trials with multiple observations for the same outcome were assessed according to randomisation and types of interventions, and separate analyses based on different periods were performed. Studies with parallel groups were included, but only data from the first phase of cross-over trials were included, due to the potential carry-over effects in the second phase.

### 3.3.14. Dealing with Missing Data

Insufficient data that were not available were reported but not included in the final analysis. We assumed the data were missing at random and only available data were analysed.

### 3.3.15. Assessment of Heterogeneity

We conducted statistical analysis, as described in the Cochrane Handbook for Systematic Reviews of Interventions (161).

### 3.3.16. Assessment of Reporting Biases

Publication bias was minimised by performing comprehensive searches of multiple databases (162). Where data were not reported in full for certain outcomes, we contacted the trial authors for the full data set or the reason for not publishing the data. Where sufficient studies (at least 10) were identified, we assessed potential biases of reporting using funnel plots and visual inspection for asymmetry according to the approach outlined in the Cochrane Handbook for Systematic Reviews of Interventions (161).

### 3.3.17. Data Synthesis

A meta-analysis was not possible due to methodological, clinical and statistically heterogeneity of included studies. We would have pooled results from clinically similar studies for the meta-analysis, if sufficient studies were available.
3.3.18. Subgroup Analysis and Investigation of Heterogeneity

Treatment effects in subgroups of trials were analysed and compared. With data that were available, we performed subgroup analysis for the following:

- sex (male/female);
- type of MS (relapsing remitting, progressive);
- Expanded Disability Status Scale (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)

3.3.19. Sensitivity Analysis

We were unable to perform sensitivity analysis because the findings from included studies evidence were too small to allow reliable analysis. Further, we were not able to pool results from chronic pain of different central origins in the primary analyses, due to lack of data.

3.3.20. Summary of findings Table

We presented the main results of the review in 'Summary of findings’ (SoF) tables (Table 8), according to recommendations described in Chapter 11 of the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0). We included an overall grading of the evidence for the following patient-important outcomes:

- reduction in pain intensity;
- reduction in disability;
- improvement in quality of life;
- reduction in fatigue;
- reduction in depression and anxiety;
- reduction in pain interference, depression, fatigue;
- improvement in pain, self-efficacy, patient activation, health-related quality of life, social role satisfaction, resilience, positive and negative affect.

We graded the quality of evidence for each outcome considering study limitations, indirectness, inconsistency, imprecision of effect estimates, and risk of reporting bias. According to the software GRADEpro 2008, we assigned four levels of quality of evidence: high, moderate, low, and very low.

3.4. Results

This section will discuss the results of this review.

3.4.1. Description of Studies

See: Characteristics of included studies in Table 7 and Characteristics of excluded studies in Table 6.
3.4.2. Results of the Search

Electronic and manual searches identified 558 references (MEDLINE =361; Embase = 138; CINAHL = 21; Central = 9; CRD database = 4; Handsearch = 7; WHO portal =4; Clinicaltrials.gov = 14). Of these 30 passed the first screening review and were selected for closer review. In total 10 articles fulfilled the inclusion criteria and were included. See Figure 12 for Study flow chart.
Figure 12. Flowchart of search methods for Cochrane review
A flowchart of search methods and included and excluded studies.
3.4.2.1. Included Studies

Overall, 10 randomised controlled trials (RCTs) (135, 163-171) involving 565 participants fulfilled the inclusion criteria for this review. Two studies were conducted in Northern Ireland (166, 171); three studies in the USA (165, 167, 168); two studies were from France (163, 172); and one study each from Spain (164), Italy (135) and Iran (169). The included studies evaluated various non-pharmacological interventions, which included:

- one study (171) evaluated the effects of TENS, which used alternating currents by cutaneous electrodes positioned near the painful area;
- two studies (135, 163) investigated the effects of tDCS, which used a low current directly delivered to the brain for neuromodulation;
- two studies (166, 169) investigated the effects of reflexology, which involves the massaging of the feet which corresponds to different parts of the body;
- one study (164) evaluated hydrotherapy;
- three studies (165, 167, 168) evaluated psychotherapy, which used a telephone-based self-management educational program, self-hypnosis and neurofeedback;
- one study (172) evaluated tRNS, which used a form of neuromodulation through rapidly changing current frequencies.

3.4.2.2. Excluded studies

Detailed descriptions of excluded studies with reason for exclusion is provided in Characteristics of excluded studies in Table 6. Overall, 20 studies were excluded (103, 173-192). Reasons for exclusion included: 13 studies did not define chronic pain as a criteria (177-179, 182-185, 187, 188, 190-192), two were abstracts only (176, 180), three were not clinical controlled trials (174, 181, 189), and two trials did not have pain as an outcome (173, 175).

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anninos 2016</td>
<td>Pain not an outcome criteria</td>
</tr>
<tr>
<td>Backus 2016</td>
<td>Not clinical controlled trial</td>
</tr>
<tr>
<td>Barlow 2009</td>
<td>Pain not an outcome criteria</td>
</tr>
<tr>
<td>Catena 2014</td>
<td>Abstract</td>
</tr>
<tr>
<td>Doultabad 2012</td>
<td>Chronic pain not a criteria</td>
</tr>
<tr>
<td>Hasanpour-Dehkordi 2016</td>
<td>Chronic pain not criteria</td>
</tr>
<tr>
<td>Hasanpour-Dehkordi 2015</td>
<td>Chronic pain not criteria</td>
</tr>
<tr>
<td>Jensen 2007</td>
<td>Abstract</td>
</tr>
<tr>
<td>Jensen 2011</td>
<td>Not controlled clinical trial</td>
</tr>
<tr>
<td>Marinelli 2014</td>
<td>Chronic pain not a criteria</td>
</tr>
<tr>
<td>Mathiowetz 2005</td>
<td>Chronic pain not a criteria</td>
</tr>
<tr>
<td>Study</td>
<td>Reason for Exclusion</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>McGuire 2015</td>
<td>Chronic pain not a criteria</td>
</tr>
<tr>
<td>Negahban 2013</td>
<td>Chronic pain not a criteria</td>
</tr>
<tr>
<td>Oken 2004</td>
<td>Chronic pain not a criteria</td>
</tr>
<tr>
<td>Pilutti 2013</td>
<td>Chronic pain not a criteria</td>
</tr>
<tr>
<td>Pozilli 2002</td>
<td>Chronic pain not a criteria</td>
</tr>
<tr>
<td>Seada 2013</td>
<td>Not controlled clinical trial</td>
</tr>
<tr>
<td>Smeadal 2011</td>
<td>Chronic pain not a criteria</td>
</tr>
<tr>
<td>Storr 2006</td>
<td>Chronic pain not a criteria</td>
</tr>
<tr>
<td>Van der Linden 2013</td>
<td>Chronic pain not a criteria</td>
</tr>
</tbody>
</table>

Table 6. Characteristics of excluded studies for Cochrane review

3.4.3. Risk of Bias in Included Studies
For a summary, refer to Table 7

3.4.3.1. Allocation (selection bias)

3.4.3.1.1. Random Sequence Generation
Nine studies were considered to have a low risk of bias for this domain (135, 163, 165-169, 171). Palm 2016 was considered to have an unclear risk of bias for this domain as randomisation not discussed (172).

3.4.3.1.2. Allocation Concealment
One study (165) was considered to have a low risk of bias for allocation concealment as the allocation sequence was concealed from the research assistants who enrolled participants via a limited access database program. The other nine studies were considered to have an unclear risk of bias for allocation concealment (135, 163, 164, 166-169, 171, 172)

3.4.3.2. Blinding (performance bias and detection bias)

3.4.3.2.1. Blinding of Participants and Personnel (Performance Bias)
Blinding of participants for performance bias was assessed as high risk in two studies (164, 167), as the study could not guarantee the study was blinded and no blinding reported, respectively. Two
studies had an unclear risk of bias (168, 169). The remaining six studies had a low risk of bias (135, 163, 165, 166, 171, 172).

3.4.3.2.2. Blinding of Participants and Personnel (Detection Bias)
Two studies were assessed as unclear risk for blinding of outcome assessment as blinding was not described (169, 172) and two studies were assessed as high risk (165, 168).

3.4.3.3. Incomplete outcome data (attrition bias)
All studies provided information on participant withdrawals and loss to follow-up. Two studies (165, 166) reported loss of participants to follow-up and were assessed as high risk; the remaining studies were considered to be at low risk of bias.

3.4.3.4. Selective Reporting (reporting bias)
All included studies assessed pre-specified primary and secondary outcomes and were assessed as 'low' risk.

3.4.3.5. Other Potential Sources of Bias
Two studies (171, 172) were assessed as unclear risk as funding was received but unclear if it had an impact on results.

3.4.4. Effects of Interventions
As aforementioned, the included studies used a wide range of non-pharmacological interventions and used various assessments relating to pain measures. Key findings based on the interventions evaluated and summary of findings are described below and tabulated in Table 4. A meta-analysis was not possible and narrative descriptions of the findings are presented instead.

3.4.4.1. Transcutaneous Electrical Nerve Stimulation (TENS)
One study (171) evaluated the effects of TENS on chronic low back pain in people with multiple sclerosis. In this study, 90 participants were randomised into three groups (N = 30 in each): low-frequency TENS, high-frequency TENS and placebo (sham). There was a decrease in low back pain scores overtime in all three groups in visual analogue scores (VAS), however, none reached statistical significance. Similarly, no statistically significant changes in the McGill Pain Questionnaire (MPQ) was found in all three groups. All three groups showed improvement in patient-reported disability scores (Roland Morris Disability Questionnaire (RMDQ)), however, it was not statistically significant.
3.4.4.2. Hydrotherapy

One RCT (N = 73 participants) (164) evaluated the effectiveness of Ai Chi water-based exercise program compared to placebo. The participants in the intervention group received Ai Chi water exercises twice a week for 20 weeks. The authors reported significant reduction in pain VAS score in the treatment group immediately after treatment (P = 0.028), which was maintained up to 30 weeks (P = 0.047). There were no statistical significance changes in the control group at any time point. Similarly, compared to the control group, the treatment group showed a significant pain reduction at week 20 in MPQ and was maintained up to week 24 (P < 0.021). There were significant decreases in disability (RMDQ) scores in both groups at week 20. The treatment group also showed a significant decrease in spasm VAS score at week 20 compared to the control group (P = 0.039). Both groups showed a significant reduction in the Multiple sclerosis Impact scale 29 (MSIS-29) psychological score at week 20.

3.4.4.3. Transcranial direct stimulation (tDCS)

Two studies (135, 163) evaluated the effectiveness of tDCS in people with MS. One RCT (163) (N = 16) randomised participants to either anodal tDCS (N = 8) or sham (N = 8) groups. The findings showed a statistically significant difference between before and after treatment for mean pain VAS scores in the treatment group (P = 0.024). There were no statistically significant changes in the sham group. Active stimulation resulted in significant improvement in pain (Brief Pain Inventory (BPI) global score) (P = 0.02), but no significant effects on severity, or in the sham group. There were no significant differences observed through stimulation for both groups for functional and psychological outcomes for MFIS and HADS.

In another study (135), participants (N = 19) were randomised to anodal tDCS (N = 10) or sham (N = 9) groups. There were statistically and clinical significant changes for pain VAS and MPQ scores in the anodal tDCS group compared to the control sham group (P < 0.05). The authors also reported statistically significant changes for the treatment effect over time in quality of life (QoL) for the Multiple Sclerosis Quality of Life-54 (MSQOL54) and the Short Form McGill Pain Questionnaire (SFMPQ). There were no statistically significant changes for other psychological outcomes (Beck Depression Inventory (BDI) and VAS for anxiety) in both groups.

3.4.4.4. Transcranial Random Noise Stimulation (tRNS)

One RCT (N = 16 participants) (172) examined the effect of tRNS in comparison with the sham. The authors found no statistically significant changes for mean pain VAS score before and after treatment for both tRNS and sham groups. There was a significant change in BPI in the treatment group but not in the sham group. Further, there were no statistically significant changes for any psychological and functional outcomes (Hospital Anxiety and Depression Scale HADS), Modified Fatigue Impact Scale (MFIS) scores) in both groups.

3.4.4.5. Psychotherapy

Three RCTs (165, 167, 168) evaluated different forms of psychotherapy. One RCT (165) (N = 163 participants) compared a telephone-delivered self-management program with the control group receiving telephone-delivered educational program. The authors reported that > 50% reduction in one or more symptoms (fatigue, pain interference and depression severity) was achieved in 58% of the intervention group and 46% of the control group. However, this was not statistically significant. There
were no clinical significant changes in pain intensity after treatment and at follow-up in both intervention and control group. The authors reported statistically significant improvements in all secondary outcomes (fatigue, self-efficacy, pain interference quality of life) for both groups, which was maintained up to six- and 12-month follow-up.

Another RCT (167) evaluating the effectiveness of self-hypnosis on pain in people with MS, randomised (N = 22) participants to self-hypnosis (N = 15) and progressive muscle relaxation (N = 7) groups. The authors found statistically and clinically significant changes pre- and post-treatment in the hypnosis group in reduction in daily pain intensity but not in the control group (P < 0.001). There was also statistically significant change pre- to post-treatment in the hypnosis group, but not in the progressive relaxation group for pain interference (P < 0.001).

Another RCT (168) randomised (N = 20) participants to the EEG biofeedback (N = 10) group or relaxation control group (N = 10). Both groups improved in pain scores soon after treatment and at one-month follow-up, however this was not statistically significant. There was a moderate to large improvement in the neurofeedback group after treatment (effect size, ES = 0.70) and 1 month after follow-up (ES = 1.04), but effect size of improvement was much lower in the control group. There were improvements for other pain scores (BPI, worst pain intensity) and fatigue severity in the intervention group with moderate to large effect size.

3.4.4.6 Reflexology

Reflexology was evaluated in two studies (166, 169). One RCT (166) (N = 71 participants) compared reflexology with a control group with sham intervention. The authors found clinical and statistically significant reduction in pain VAS scores at 10 weeks compared to baseline in both groups (P = 0.0001), which was maintained up to 22 weeks. Both groups demonstrated significant reduction in MPQ pain rating index at week 10. For MPQ pain index there were no changes in the sham group, but a statistically significant change at week 10 for the reflexology group (P < 0.012). Both groups showed a significant reduction in disability score measured by RMDQ at 10 weeks. Further, both groups had a similar statistically significant decrease in VAS spasms score by the end of the treatment period. Both groups showed significant reductions in psychology and physical subscales of MSIS at week 10. There was a significant reduction by week 10 in both groups in fatigue (MFIS, Fatigue Severity Scale (FSS) scores), with no significant differences between groups. There was a significant reduction in psychological outcomes (BDI scores) by week 10 in both groups. Functional improvements (measured by the Barthel Index (BI)) in both groups remained stable throughout treatment by week 10.

Another RCT (169) (N = 75 participants) randomised participants to either reflexology, relaxation or control groups. There were statistically and clinical significant differences in pain scores in the reflexology group (P < 0.001) and relaxation group (P = 0.01) pre- and post-treatment, while no significant changes were found in the control group (P = 0.34).

<table>
<thead>
<tr>
<th>Ayache 2016</th>
</tr>
</thead>
</table>
| **Methods** | • Randomised sham-controlled trial, cross-over and double blinded study  
• Randomisation through computer generation  
• Study conducted in France |
### Participants

**Population source:** Participants enrolled from Neurology Department of Henri Mondor Hospital.

**Numbers:** Randomised: 16, anodal transcranial direct current stimulation: 8, sham: 8

**Inclusion criteria:** Age 18-70, definitively diagnosed with multiple according to McDonalds Criteria, right-handedness based on Edinburgh Inventory, neuropathic pain >3 months as per Neuropathic Pain Symptom Inventory, VAS>40 over average 1 week

**Exclusion criteria:** Multiple sclerosis relapses within last 2 months, changes in pharmacological and physiotherapy in last month, presence of comorbid neurodegenerative or psychiatric disorders, history of substance abuse, absence of measurable pain related evoked potentials at right hand, severe deficits in visual acuity and fields by exam, severe upper limb impairment by Medical Research Council for muscle power.

**Age:** Mean age 48.9 years, range 38-67 years

**Gender:** women 13, men 3

**Type of MS:** Relapsing remitting 11, secondary progressive 4, primary progressive 1

**Pain type:** Neuropathic pain

### Interventions

**Treatment:** Anodal tDCS, 2mA current

**Control:** Sham tDCS

**Duration:** 3 consecutive days of tDCS stimulation (20min sessions), at least 3 weeks washout period

### Outcomes

- Visual Analogue Scale (VAS)
- Brief Pain Inventory (BPI)
- Modified Fatigue Impact Scale (MFIS)
- Hospital Anxiety and Depression Scale (HADS)
- Comfort Rating Questionnaire (CRQ)
- Clinical Global Impression (CGI)

### Notes

**Funding:** Authors had received grants and gave lectures.

**Conflicts of interest:** Authors declared no commercial of financial relationships that could act as conflict of interest

### Risk of Bias

<table>
<thead>
<tr>
<th>Author’s Judgement</th>
<th>Support for Judgement</th>
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<tbody>
<tr>
<td><strong>Random sequence generation (selection bias)</strong></td>
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</tr>
<tr>
<td><strong>Allocation concealment (selection bias)</strong></td>
<td>Unclear risk</td>
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<td><strong>Blinding of participants and personnel</strong></td>
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<td>(performance bias)</td>
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<td><strong>Blinding of outcome assessment (detection bias)</strong></td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>Incomplete outcome data (attrition bias)</strong></td>
<td>Low risk</td>
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<tr>
<td><strong>Selective reporting (reporting bias)</strong></td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>Other bias</strong></td>
<td>Low risk</td>
</tr>
</tbody>
</table>

| Castro-Sanchez 2012 |
|---|---|
| **Methods** | - Randomised controlled trial  
- Study conducted in Spain  
- Randomisation through computer-generation  
- Allocation concealment not described |
| **Participants** | **Population source:** Participants were recruited from MS Association of Almeria in Spain.  
**Numbers:** Randomised:73, Ai Chi:36, control:37  
**Inclusion criteria:** MS diagnosis, age between 18 and 75 yrs, VAS pain score >4 for at least two months, EDSS≤7.5  
**Exclusion criteria:** Treatment with another complementary and alternative medicine (either current or within the previous 3 month, relapse requiring hospitalisation or steroid treatment within the past 2 months  
**Age:** Experimental group (mean age 46, range 25-75), control group (mean age 50, range 29-75)  
**Gender:** Experimental group (26 women,10 men), control group (24 women,13 men)  
**Type of MS:** Experimental group (6 primary progressive,9 secondary progressive, 21 unknown),control group (9 primary progressive, 12 secondary progressive, 16 unknown)  
**Pain type:** Musculoskeletal pain (back,cervical,legs,feet,arms,shoulder) |
| **Interventions** | **Treatment:** Ai Chi exercises  
**Control:** Relaxation  
**Duration:** 20 weeks (twice a week), 4 sessions |
| **Outcomes** | **Primary**  
- Pain Visual Analogue Scale (VAS)  
- McGill Pain Questionnaire (MPQ)  
- Roland Morris Disability Questionnaire (RMDQ)  
**Secondary**  
- Spasm Visual Analogue Scale (VAS)  
- Multiple sclerosis Impact scale 29 (MSIS29)  
- Modified Fatigue Impact Scale (MFIS) |
Fatigue Severity Scale (FSS)

Notes

Funding: Not described
Conflicts of interest: Not described

Risk of Bias

<table>
<thead>
<tr>
<th>Author’s Judgement</th>
<th>Support for Judgement</th>
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<td>Random sequence generation (selection bias)</td>
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<tr>
<td>Incomplete outcome data (attrition bias)</td>
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<td>Selective reporting (reporting bias)</td>
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</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

Ehde 2015

Methods

- Randomised controlled trial, single blinded, parallel group and single centre
- Study conducted in USA
- Randomisation through computer-generation
- Allocation by limited access database program

Participants

Population source: Recruited from University of Washington Department of Rehabilitation Medicine Research, Registry and advertisements through National MS organisations. Flyers and referrals from University of Washington Multiple Sclerosis Centre.

Numbers: Randomised: 163, telephone self-management: 75, control (telephone education): 88

Inclusion criteria: >18 years, self-reported physician diagnosis of MS
and 1 or more of the following: (1) moderate depressive symptoms indicated by a score of 10 to 14 on the PHQ-9, presence of chronic pain (average pain intensity 3 in the past week) or significant fatigue symptoms, defined as a score 10 on the 5-item (modified fatigue impact scale)

**Exclusion criteria:** Cognitive impairment (1 error on 6-item Cognitive Screener), psychotherapy more than once a month, had participated in another study for fatigue, depression, or pain, moderate-severe to severe depressive symptoms (PHQ-9:score 15)  
**Age:** Treatment group (mean age 51, range 25-76), control group (mean age 53.2, range 26-76)  
**Gender:** Treatment group (women 67, men 8), control group (women 75, men 13)  
**Type of MS:** Treatment group (relapsing remitting 46, progressive 29), control group (relapsing remitting 45, progressive 43)  
**Pain type:** Chronic pain

### Interventions
- **Treatment:** Telephone self-management skills training  
- **Control:** Education on MS symptoms  
- **Duration:** 8 weekly individual telephone delivered, 45-60 minute sessions

### Outcomes
- **Primary**  
  - Modified Fatigue Impact Scale (MFIS)  
  - Brief Pain Inventory (BPI)  
  - Patient Health Questionnaire-9 (PHQ-9)  
- **Secondary**  
  - Pain Numeric Rating Scale (Pain NRS)  
  - Self-Efficacy Scale (SES)  
  - Positive and Negative Affect Scale (PANAS)  
  - Patient Activation Measure (PAM)  
  - Short Form 8 Health Survey (SF8)  
  - Patient Reported Outcomes Measurement Information System  
  - Conner Davidson Resilience Scale

### Notes
- **Funding:** Not described  
- **Conflicts of interest:** Not described

### Risk of Bias

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<td>The allocation sequence was concealed from the research assistants who enrolled participants via a limited access database program</td>
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<tr>
<td>Blinding of participants and personnel</td>
<td>Low risk</td>
<td>On 2 occasions research assistants became aware of a participant’s allocation</td>
</tr>
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</table>
(performance bias) |  |  |
---|---|---
Blinding of outcome assessment (detection bias) | High risk | On 2 occasions research assistants became aware of a participant’s allocation |
Incomplete outcome data (attrition bias) | High risk | For the telephone self-management group there were 10 withdrawals during sessions and 4 during assessments. For the control group there were 6 withdrawals during sessions and 2 withdrawals during assessments |
Selective reporting (reporting bias) | Low risk | All outcomes reported |
Other bias | Low risk | No other bias detected |

#### Hughes 2009

**Methods**
- Randomised controlled trial, double blinded
- Study in Northern Ireland
- Randomisation through computer generated lists
- Allocation concealment not described

**Participants**

Population source: Responses to advertisement in local advertisement and MS charities.
Numbers: Randomised: 71, intervention: 35, sham: 36
Inclusion criteria: 18–75 years of age, definite diagnosis of MS, pain greater than 4 on visual analogue scale of at least 2 months, EDSS of 7.5
Exclusion criteria: Previous experience of reflexology, participation in research studies currently or within the previous 3 months, relapse (requiring hospitalisation or steroid treatment) within the past 2 months
Age: Reflexology group (mean age 50, range 26–75), sham group (mean age 53, range 34–74)
Gender: Reflexology group (30 women, 5 men), sham group (29 women, 7 men)
Type of MS: Precision reflexology group (benign 0, relapsing remitting 16, primary progressive 4, secondary progressive 6, unknown 9), sham group (benign 1, relapsing remitting 12, primary progressive 4, secondary progressive 13, unknown 6)
Pain type: Musculoskeletal (low back pain, legs, feet, shoulders, hips, arms, eye)

**Interventions**

Intervention: Reflexology by accredited reflexology specialist.
Control: Standardised foot massage
Duration: 45 minute sessions weekly for 10 weeks

**Outcomes**

Primary
- Visual Analogue Scale (Pain)
<table>
<thead>
<tr>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Visual Analogue Scale (weekly pain scores) (VAS)</td>
</tr>
<tr>
<td>● McGill Pain Questionnaire (MPQ)</td>
</tr>
<tr>
<td>● Pain Rating Index (PRI)</td>
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<tr>
<td>● Present Pain Intensity (PPI)</td>
</tr>
<tr>
<td>● Roland Morris Disability Questionnaire (RMDQ)</td>
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<tr>
<td>● Visual Analogue Scale (Spasticity) (VAS)</td>
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<tr>
<td>● Multiple Sclerosis Impact Scale-29 (MSIS29)</td>
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<tr>
<td>● Modified Fatigue Impact Scale (MFIS)</td>
</tr>
<tr>
<td>● Fatigue Severity Score (FSS)</td>
</tr>
<tr>
<td>● Becks Depression Inventory 2 (BDI2)</td>
</tr>
<tr>
<td>● Barthel Index</td>
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**Notes**

**Funding:** National MS Society, USA and Action MS for their assistance with recruitment and the use of facilities  
**Conflicts of interest:** None to declare

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<th>Support for Judgement</th>
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<td>Participants were blinded to group allocation</td>
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<td><strong>Blinding of outcome assessment (detection bias)</strong></td>
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<td>Investigator who was blinded to group allocation</td>
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<td><strong>Incomplete outcome data (attrition bias)</strong></td>
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<td>There were 5 participants lost to follow up</td>
</tr>
<tr>
<td><strong>Selective reporting (reporting bias)</strong></td>
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<td>All outcomes in the review reported</td>
</tr>
<tr>
<td><strong>Other bias</strong></td>
<td>Low risk</td>
<td>No other bias detected</td>
</tr>
</tbody>
</table>

**Jensen 2009**

**Methods**

● Randomised controlled clinical trial
- Study conducted in USA
- Randomisation through computer-generated lists
- Allocation concealment not described

| Participants | Population source: Recruited from previously completed survey of study of pain  
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 0–10 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 of 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.  
Age: Mean age 51.7 years (27-75 years)  
Gender: 16 women, 6 men  
Type of MS: Not reported  
Pain type: Not reported |
|---|---|
| Interventions | Intervention: Self-hypnosis training  
Control: Progressive relaxation  
Duration: 10 sessions |
| Outcomes | Primary outcome  
- Numerical Rating Scale (NRS)  
Secondary outcomes  
- Brief Pain Inventory (BPI)  
- Amount and effects of hypnosis (pain relief 0-10, number of days listened, usual number of times listened, hours of relief they experiences after listening) |
| Notes | Funding: Not reported  
Conflicts of interest: Not reported |
<p>| Risk of Bias | Author’s Judgement | Support for Judgement |
| Random sequence generation (selection bias) | Low risk | Participants were randomly assigned via a computer-generated list of random numbers |
| Allocation concealment (selection bias) | Unclear risk | No allocation concealment described |
| Blinding of participants and personnel | High risk | No blinding reported |</p>
<table>
<thead>
<tr>
<th>(performance bias)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blinding of outcome assessment (detection bias)</strong></td>
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<tr>
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<tr>
<td><strong>Selective reporting (reporting bias)</strong></td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>Other bias</strong></td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**Jensen 2016**

**Methods**
- Randomised controlled trial
- Study conducted in USA
- Randomisation through computer-generated lists
- Allocation concealment not described

**Participants**

| Population source: | Recruited from former participants of an ongoing MS symptom self-management study (that did not receive intervention), University of Washington Medical Centre (UWMC) MS Clinic, Harborview and/or UWMC Rehabilitation Clinic and self-referrals from study brochures and flyers. |
| Numbers: | Randomised 20, EEG biofeedback (NF-HYP):10, relaxation control group:10 |
| 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 0–10 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, hospitalization or psychiatric reasons in the past 6 months, or failure to pass a cognitive screening test and experiencing an MS exacerbation. |
| Age: | Mean age (50 years) |
| Gender: | 12 women, 7 men |
| Type of MS: | Relapsing remitting 12, secondary progressive 5, primary progressive 0, progressive relapsing 0, unknown 2 |
| Pain type: | Not reported |
| Adverse effects: | Not reported |

**Interventions**

<p>| Intervention: | Hypnosis preceded by neurofeedback |
| Control: | Hypnosis preceded relaxation |
| Duration: | 5 sessions of self-hypnosis training (1 face to face and 4 pre-recorded sessions) |
| Neurofeedback: | 20 minutes of neurofeedback |</p>
<table>
<thead>
<tr>
<th>Relaxation: 20 minutes of relaxation through headphones</th>
</tr>
</thead>
</table>
| **Outcomes** | **Primary outcomes**  
- Numerical Rating Scale (Average) (NRS)  
**Secondary outcomes**  
- Numerical Rating Scale (Worst pain intensity) (NRS)  
- Fatigue Severity Scale (FSS)  
- Brief Pain Inventory (BPI) |
| **Notes** | **Funding:** Not reported  
**Conflicts of interest:** Not reported |
| **Risk of Bias** | **Author’s Judgement** | **Support for Judgement**  
| Random sequence generation (selection bias) | Low risk | Randomisation through computer generated numbers  
| Allocation concealment (selection bias) | Unclear risk | No allocation concealment described  
| Blinding of participants and personnel (performance bias) | Unclear risk | Blinding was not described  
| Blinding of outcome assessment (detection bias) | High risk | No blinding for assessors  
| Incomplete outcome data (attrition bias) | Low risk | 1 subject data not collected  
| Selective reporting (reporting bias) | Low risk | All outcomes reported  
| Other bias | Low risk | No other bias detected |

<table>
<thead>
<tr>
<th>Mori 2010</th>
</tr>
</thead>
</table>
| **Methods** | Randomised controlled trial and double blinded  
- Study conducted in Italy  
- Randomisation through computer-generated lists  
- Allocation concealment not described |
| **Participants** | **Population source:** Randomised:19, intervention group (transcranial direct current stimulation):10, control:9 |
**Inclusion criteria:** Diagnosis of MS established by McDonald’s Criteria, chronic neuropathic pain >1 month (stereotyped neurological distribution and superficial location), Visual Analogue Scale ≥4

**Exclusion criteria:** Pain relating to spasticity

**Age:** Mean age 44.8

**Gender:** women 11, men 8

**Pain type:** Neuropathic pain

**Type of MS:** Not reported

**Interventions**

**Treatment:** Anodal tDCS, 2mA current

**Control:** Sham tDCS

**Duration:** 5 consecutive daily stimulation (20 minute sessions)

**Outcomes**

- Visual analogue scale (Pain) (VAS)
- Visual analogue scale (Anxiety) (VAS)
- Short Form McGill Pain Questionnaire (SFMPQ)
- Multiple Sclerosis Quality of Life-54 (MSQOL54)
- Beck Depression Inventory (BDI)

**Notes**

**Funding:** None to declare

**Conflicts of interest:** None to declare

**Risk of Bias**

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<td>Patients and assessing physician were blinded to group allocation</td>
</tr>
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<td>Blinding of outcome assessment (detection bias)</td>
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<td>Patients and assessing physician were blinded to group allocation</td>
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<td>None lost to follow up</td>
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<td>Low risk</td>
<td>All outcomes in the review reported</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No other bias detected</td>
</tr>
</tbody>
</table>
## Nazari 2010

### Methods

- Randomised control trial, single blinded
- Study conducted in Iran
- Randomisation through computer-generated lists
- Allocation concealment not described

### Participants

**Population source:** MS patients referred to the Clinic of Ayatollah Kashani Hospital (Isfahan, Iran) in 2014,

**Numbers:** Randomised: 75, relaxation: 25, reflexology: 25, control: 25

**Inclusion criteria:** Female, definite diagnosis of MS, 18–75 years of age, healthy legs, not suffering from diseases other than MS, willing to participate in the study, not having a drug addiction, not being pregnant, not being a medical staff, feeling chronic pain in at least one body organ, having a history of pain medication use, NRS ≥4 for at least 6 months, expanded disability status scale of 0–7.5

**Exclusion criteria:** Receiving other complementary and alternative treatment during the study period and reflexology treatment, receiving formal training and practicing relaxation in the previous 6 months, acute relapse 1 month preceding or during the study period, not wanting to continue their cooperation in the research

**Age:** Reflexology group (mean 34.4), relaxation (mean 33.9), control group (mean 34.4)

**Gender:** Female only

**Type of MS:** Relapsing remitting (reflexology 88%, relaxation 84%, control: 80%)

### Interventions

**Treatment:** Relaxation (Audio tape guided relaxation), reflexology (General reflexology massage technique)

**Control:** Routine care 4 weeks

**Duration:** Twice a week, each session lasting 40 minutes

### Outcomes

- Pain NRS

### Notes

**Funding:** Research conducted under financial support of the Vice Chancellor for Research of Isfahan University of Medical Sciences.

**Conflicts of interest:** None to declare

### Risk of Bias

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<tr>
<td>Other bias</td>
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</table>

**Palm 2016**

**Methods**
- Randomised controlled, cross over, double blinded trial
- Study conducted in France
- Randomisation method not discussed
- Allocation concealment not discussed

**Participants**

**Population source**: MS patients recruited from inpatient and outpatient neurology departments at Henri Mondor hospital, Creteil, France.

**Numbers**: Randomised: 16 (not reported number in each group)

**Inclusion criteria**: Age 18-70 years of age, right handedness as per Edinburgh Inventory, a definitive diagnosis of MS according to McDonald’s Criteria, presence of neuropathic pain as per neuropathic pain symptom inventory > 3 months, Visual Analogue Scale (0-100) > 40 mm on a daily basis during a representative week, a stable pharmacological and physical therapies since at least 1 month, the presence of measurable pain related evoked potentials at the right hand, the absence of MS relapses within the last 2 months and other neurological or psychiatric conditions.

**Exclusion criteria**: Patients unable to perform the attention network test, deficits in visual fields or severe upper limb impairment based on medical research council scale score of less than 12

**Age**: Mean age: 47.4 years, age range 38-64 years

**Gender**: 13 women, 3 men

**Type of MS**: 11 relapsing remitting, 4 secondary progressive, 1 primary progressive
Pain type: Neuropathic pain  
**Adverse effects:** Phosphenes (1 sham), insomnia (6 sham, 5 treatment), nausea (4 sham, 2 treatment), headache (1 sham)

| Interventions | Treatment: Transcranial random noise stimulation (tRNS)  
Control: Sham controlled  
**Duration:** 3 daily consecutive sessions of sham or tRNS |
|---|---|

| Outcomes | ● Visual Analogue Scale (VAS)  
● Brief Pain Inventory (BPI)  
● Attention Network Test (ATN)  
● Hospital Anxiety and Depression Scales (HADS)  
● Modified Fatigue Impact Scale (MFIS)  
● Pain Related Evoked Potentials (PREP)  
● Frontal Midline Theta Activity (FMTA) |
|---|---|

| Notes | **Funding:** Received grants  
**Conflicts of interest:** None |
|---|---|

| Risk of Bias | Author’s Judgement  
Support for Judgement |
|---|---|
| Random sequence generation (selection bias) | Unclear risk  
Randomisation not discussed |
| Allocation concealment (selection bias) | Unclear risk  
Allocation concealment not described |
| Blinding of participants and personnel (performance bias) | Low risk  
Blinding was achieved |
| Blinding of outcome assessment (detection bias) | Unclear risk  
Blinding of assessors was not described or if it was achieved |
| Incomplete outcome data (attrition bias) | Low risk  
None lost to follow-up |
| Selective reporting (reporting bias) | Low risk  
All outcomes reported |
| Other bias | Unclear risk  
Received grants, not discussed if affected results |

Warke 2006
### Methods
- Randomised controlled trial, single blinded
- Study conducted in Northern Ireland
- Randomisation through computer-generated lists
- Allocation concealment not described

### Participants
**Population source:** Recruited from MS hospital clinics and various within Northern Ireland.

**Numbers:** Randomised: 90, low frequency (4hz); 30, high frequency (110hz); 30, placebo: 30

**Inclusion criteria:** 18-80 years, chronic (>3 months), stable lumbar back pain, participants undergoing concomitant treatments and stable for 30 days before and throughout the duration of the trial

**Exclusion criteria:** Comorbidity including serious spinal pathology and/or psychosocial risk factors, acute MS relapse 1 month preceding or during the trial period, any contraindication to TENS, judged not competent to give informed consent, analgesic abuse, sacral pressure ulcers, participation in other research studies within the previous 3 months

**Age:** Range 21-78, Low frequency (mean 45.6), high frequency (mean 47.8), placebo (mean: 48.7)

**Gender:** Low frequency (24 women, 6 men), high frequency (22 women, 8 men), placebo: 23 women, 7 men

**Type of MS:** Not reported

**Pain type:** Low back pain

### Interventions
**Treatment:** Low frequency (4hz), high frequency (110hz), Control: Placebo TENS

**Duration:** Lumbar spine application, ≥ twice daily application, 45 minutes for 6 weeks and anytime pain occurred.

### Outcomes
**Primary**
- Visual Analogue Scale (Average) (VAS)
- McGill Pain Questionnaire (MPQ)

**Secondary**
- Visual Analogue Scale lumbar (Worst) (VAS)
- Roland Morris Disability Questionnaire (RMDQ)
- Barthel Index (BI)
- Rivermead Mobility Index (RMI)
- Multiple Sclerosis Quality of Life 54 (MSQOL54)

### Notes
**Funding:** Financial support from MS Society of Great Britain and Northern Ireland

**Conflicts of interest:** No other conflicts of interest listed

### Risk of Bias

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<th>Author’s Judgement</th>
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<tr>
<td><strong>Selective reporting (reporting bias)</strong></td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>Other bias</strong></td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

**Table 7. Characteristics of included studies for Cochrane review**

A summary of characteristics of included studies including a summary of methods, participants, interventions, outcomes and risk of bias. There was a total of 10 included studies summarised.

**3.5. Discussion**

Discussion of the summary of results and evidence of this review.

**3.5.1 Summary of Main Results**

Overall, 10 RCTs with 565 participants fulfilled the inclusion criteria of this review, which evaluated various non-pharmacological interventions for the management of chronic pain in persons with multiple sclerosis, which included: physical therapy (Ai Chi water exercise), psychotherapy (telephone self-management, cognitive restructuring, neurofeedback and hypnosis), neuromodulatory techniques (transcranial direct stimulation (tDCS), transcranial random noise stimulation (tRNS)), reflexology and transcutaneous electrical nerve stimulation (TENS). The included trials were heterogeneous in terms of: type and intensity of interventions evaluated and outcome measures used. The study quality varied and formulating pooled evidence was limited due to high risk of bias, underpowered studies (small sample size) and lack of data on changes of pain outcomes in majority of the studies. Therefore, quantitative synthesis was not possible and a qualitative synthesis of 'best evidence' was summarised in Table 8.

The findings suggest that there is 'very low level' evidence for the following interventions.

- TENS in reducing lower back pain.
- Ai Chi water exercises in improving pain intensity which was maintained up to 30 weeks. There were also improvements in spasm, quality of life (QoL) and fatigue.
- tDCS in reduction in pain intensity and up to three weeks after treatment and improvement in QoL, but not in fatigue and anxiety and depression.
- tRNS in improving pain scores, depression or anxiety or fatigue.
- Telephone-delivered self-management program for the reduction of pain intensity, catastrophisation, self-efficacy, fatigue and QoL in chronic pain.
- EEG biofeedback for reduction in pain intensity and fatigue and pain interference.
- Reflexology in reducing pain intensity, disability, fatigue, psychological and physical impact and depression up to 22 weeks.

### Transcutaneous Electrical Nerve Stimulation (TENS) compared to Sham for Chronic Back Pain in Multiple Sclerosis

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Impact</th>
<th>Number of Participants</th>
<th>Certainty of Evidence</th>
</tr>
</thead>
</table>
| Reduction in pain intensity assessed with: VAS, MPQ | Decrease in low back pain scores overtime for all groups, however, none reached clinical or statistical significance in VAS scores. No statistically significant changes in MPQ (171). VAS mean reduction for TENS low frequency at week 6 was -16.59 (weekly low back pain) and -19.76 (average low back pain). | 90 (1 RCT) | VERY LOW

| Reduction in disability assessed with: RMDQ, BI | No significant changes in disability measured by RMDQ and BI between treatment and placebo groups and within-groups (171). | 90 (1 RCT) | VERY LOW

| Quality of Life assessed with: LMSQoLQ, SF-36 | No significant difference in quality of life measured by MSQoLQ or SF-36 between treatment and placebo groups (171). | 90 (1 RCT) | VERY LOW

BI: Barthel Index; MPQ: McGill Pain Questionnaire; LMSQoLQ: Leeds Multiple Sclerosis Quality of Life Questionnaire; RMDQ: Roland Morris Disability Questionnaire,; SF-36: Short Form 36; VAS: Visual Analog Scale

Footnotes:
1 Downgraded two levels due to high risk for bias (unclear allocation concealment)
2 Downgraded two levels due to high risk of bias for imprecision (singular study of small sample size)

### Ai Chi Exercises compared to sham for chronic musculoskeletal pain in Multiple Sclerosis
**Patient or population:** Chronic musculoskeletal pain in MS  
**Setting:** Participants were recruited from MS Association of Almeria in Spain  
**Intervention:** Ai Chi Exercises  
**Comparison:** Sham

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Impact</th>
<th>Number of Participants</th>
<th>Certainty of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in pain intensity assessed with: VAS, MPQ</td>
<td>Significant reduction in pain scores measured by VAS in the treatment group immediately after treatment and no significant change from baseline in the control group. Pain VAS at week 20 was 50% (experimental) and 23% (control). Significant pain reduction for MPQ in the treatment group and no significant change from baseline in the control group (164).</td>
<td>73 (1 RCT)</td>
<td><img src="image1" alt="Image" /></td>
</tr>
<tr>
<td>Reduction in disability assessed with: RMDQ</td>
<td>Significant reduction in disability measured by RMDQ in intervention and control group at week 20 (164)</td>
<td>73 (1 RCT)</td>
<td><img src="image2" alt="Image" /></td>
</tr>
<tr>
<td>Quality of Life assessed with: MSIS-29</td>
<td>Both groups showed a significant reduction in the psychological sub scale of the MFIS at week 20. Treatment group showed significant score reduction but the control group showed no significant difference with baseline score in the physical sub scale at week 20 (164).</td>
<td>73 (1 RCT)</td>
<td><img src="image3" alt="Image" /></td>
</tr>
<tr>
<td>Reduction in Fatigue assessed with: MFIS</td>
<td>Treatment group showed a significant score reduction compared with baseline at week 20, but no significant difference in control group. Treatment group showed a significant reduction in cognitive scale compared with the control group (164).</td>
<td>73 (1 RCT)</td>
<td><img src="image4" alt="Image" /></td>
</tr>
</tbody>
</table>

MFIS: Modified Fatigue Impact Scale; MPQ: McGill Pain Questionnaire; MSIS-29: Multiple Sclerosis Impact Scale-29; RMDQ: Roland Morris Disability Questionnaire, SF-36: Short Form 36; VAS: Visual Analog Scale

Footnotes:  
1 Downgraded two levels because the singular study was considered at serious risk of performance bias (blinding of participants and personal) and unclear risk of allocation concealment  
2 Downgraded two levels due to imprecision (small sample size)

**Transcranial Direct Current Stimulation compared to sham for chronic neuropathic pain in Multiple Sclerosis**
### Patient or population: Chronic neuropathic pain in MS
### Setting: Multiple Sclerosis
### Intervention: Transcranial Direct Current Stimulation
### Comparison: Sham

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Impact</th>
<th>Number of Participants</th>
<th>Certainty of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in Pain Intensity assessed with: VAS, BPI, MPQ</td>
<td>Mean pain VAS showed significant decrease after active tDCS (mean baseline 51.2; after treatment 43.1) but no significant change after sham (mean baseline 52.1; after treatment 50.3). BPI global score for active tDCS resulted in significant improvement on the interference sub scale but no significant effects on the severity sub scale (163). Significant main effect of time for daily pain VAS (135).</td>
<td>35 (2 RCTs)</td>
<td>VERY LOW 1, 2</td>
</tr>
<tr>
<td>Reduction in fatigue assessed with: MFIS</td>
<td>There was no significant difference in fatigue measured by the MFIS between groups (163)</td>
<td>16 (1 RCT)</td>
<td>VERY LOW 1, 2</td>
</tr>
<tr>
<td>Reduction in depression and anxiety assessed with: BDI, HADS, VAS for anxiety</td>
<td>No significant differences in depression and anxiety were observed for both groups on HADS (163). No significant changes for BDI and VAS for anxiety with time as within subjects and group of treatment as between subjects (135)</td>
<td>35 (2 RCTs)</td>
<td>VERY LOW 1, 2</td>
</tr>
<tr>
<td>Improvement in QoL assessed with: MSQOL54</td>
<td>Significant effect of time and group x time interaction for quality of life measured by the MSQOL54 (135)</td>
<td>19 (1 RCT)</td>
<td>VERY LOW 1, 2</td>
</tr>
</tbody>
</table>

BDI: Beck Depression Inventory; HADS: Hospital Anxiety and Depression Scale; MPQ: McGill Pain Questionnaire; MSQOL54: Multiple Sclerosis Quality of Life 54. QoL: Quality of life, VAS: Visual Analog Scale

Footnotes
1 Downgraded one level for risk for bias (the two studies at unclear risk of bias in allocation concealment)
2 Downgraded two levels for high risk for imprecision (small sample sizes of both studies)
### Transcranial Random Noise Stimulation compared to sham for chronic neuropathic pain in Multiple Sclerosis

**Patient or population:** Chronic neuropathic pain in MS  
**Setting:** Hospital MS clinics  
**Intervention:** Transcranial Random Noise Stimulation  
**Comparison:** Sham

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Impact</th>
<th>Number of Participants</th>
<th>Certainty of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in pain assessed with:</td>
<td>No statistically significant changes for mean VAS treatment (mean VAS</td>
<td>16</td>
<td>1 RCT</td>
</tr>
<tr>
<td>VAS, BPI</td>
<td>before 50.1; mean VAS after 47.2) and sham groups (mean VAS before:</td>
<td></td>
<td><strong>VERY LOW</strong></td>
</tr>
<tr>
<td></td>
<td>52.1; mean VAS after:50.3). No statistical significance before and after stimulation sham and treatment for BPI (172).</td>
<td></td>
<td>1, 2</td>
</tr>
<tr>
<td>Reduction in anxiety and depression assessed with: HADS</td>
<td>No statistical significance before and after for treatment and sham for mean HADS (172).</td>
<td>16</td>
<td>1 RCT</td>
</tr>
<tr>
<td>Reduction in fatigue assessed with: MFIS</td>
<td>No statistical significance before and after sham and treatment for mean total score (172).</td>
<td>16</td>
<td>1 RCT</td>
</tr>
</tbody>
</table>

BPI: Beck Pain Inventory; HADS: Hospital Anxiety and Depression Scale; MFIS: Modified Fatigue Impact Scale; VAS: Visual Analog Scale

**Footnotes**

1. Downgraded two levels because the singular study was considered at high risk of bias (unclear risk of bias in randomisation sequence generation, allocation concealment and blinding of outcome assessors)
2. Downgraded two levels due to high risk for imprecision (singular study of small sample size)

### Telephone delivered education compared to sham for chronic pain in Multiple Sclerosis

**Patient or population:** Chronic pain in Multiple Sclerosis  
**Setting:** Participant’s home across United States  
**Intervention:** Telephone Delivered Education Group  
**Comparison:** Sham

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Impact</th>
<th>Number of Participants</th>
<th>Certainty of Evidence</th>
</tr>
</thead>
</table>

68
Reduction in pain interference, depression, fatigue assessed with: BPI, PHQ-9, MFIS

<table>
<thead>
<tr>
<th>Project</th>
<th>Description</th>
<th>Participants</th>
<th>Certainty of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>58% of telephone self-management group and 46% of telephone education group had &gt;50% reduction in 1 or more symptoms (fatigue, pain, depression) but not statistically significant (165).</td>
<td>163 (1 RCT)</td>
<td>VERY LOW 1, 2</td>
<td></td>
</tr>
</tbody>
</table>

Improvement in pain, self-efficacy, patient activation, health-related quality of life, social role satisfaction, resilience, positive and negative affect assessed with: Average Pain Intensity, UWSES, Patient Activation Measure, Medical Outcomes Study 8 Item Short Form Heath Survey, Patient Reported Outcomes Measurement Information System Short-Form, Connor-Davidson Resilience Scale

<table>
<thead>
<tr>
<th>Project</th>
<th>Description</th>
<th>Participants</th>
<th>Certainty of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statistically significant improvements in all secondary outcomes for fatigue, pain interference, self-efficacy and QoL compared with telephone education group (165).</td>
<td>163 (1 RCT)</td>
<td>VERY LOW 1, 2</td>
<td></td>
</tr>
</tbody>
</table>

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Footnotes:
1 Downgraded two levels due to high risk of bias (singular study at high risk of bias in blinding of outcome assessor and attrition)
2 Downgraded two levels due to high risk of bias for imprecision (small sample size)

---

**Hypnosis compared to relaxation/control for chronic pain in Multiple Sclerosis**

**Patient or population:** Chronic pain in MS  
**Setting:** MS clinics  
**Intervention:** Hypnosis  
**Comparison:** Relaxation/control

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Impact</th>
<th>Number of Participants</th>
<th>Certainty of Evidence</th>
</tr>
</thead>
</table>
Reduction in pain intensity assessed with: Average Pain Intensity, Daily Pain Intensity (Numeric Rating Scale) | Statistically significant changes pre and post treatment for hypnosis group but not in progressive relaxation group. Statistically significant decrease in daily/average pain scores for the self-hypnosis group but not significant in the progressive muscle relaxation group (167). | 22 (1 RCT) | VERY LOW 1, 2

Reduction in pain interference assessed with: BPI | Statistically significant change pre to post treatment in the hypnosis group but not in the progressive relaxation group (167). | 22 (1 RCT) | VERY LOW 1, 2

BPI: Brief Pain Inventory

Footnotes:
1 Downgraded two levels due to high risk for bias (the singular study did not describe whether blinding had occurred for participants)
2 Downgraded two levels due to high risk for imprecision (singular study of small sample size)

Neurofeedback compared to relaxation/control for chronic pain in Multiple Sclerosis

Patient or population: Chronic pain in MS
Setting: MS clinics
Intervention: Neurofeedback
Comparison: Relaxation/control

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Impact</th>
<th>Number of Participants</th>
<th>Certainty of Evidence</th>
</tr>
</thead>
</table>
| Reduction in pain intensity assessed with: Numerical Rating Scale (average) | Both groups improved soon after intervention and at 1 month follow-up, but not statically significant. Average mean pain intensity for intervention (before 5.30; after: 4.41; 1 month 3.98) and control (before 5.24; after 4.32; 1 month 4.31). Worst pain intensity score improvements in intervention (before 6.68; after 5.90; 1 month 5.18) and control (before 6.38; after 5.49; 1 month 5.35) (168). | 20 (1 RCT) | VERY LOW 1, 2

| Reduction in fatigue assessed with: FSS | Improvements over time pre to post treatment in intervention (168). | 20 (1 RCT) | VERY LOW 1, 2 |
Reduction in pain interference assessed with: BPI | BPI score improvement in both groups (168). | 20 (1 RCT) |  

BPI: Brief Pain Inventory; FSS: Fatigue Severity Scale

Footnotes:
1 Downgraded two levels due to high risk for bias (unclear allocation concealment and no blinding of outcome assessors)
2 Downgraded two levels due to high risk for imprecision (singular study of small sample size)

<table>
<thead>
<tr>
<th>Reflexology compared to sham for chronic pain in Multiple Sclerosis</th>
</tr>
</thead>
</table>

**Patient or population:** Chronic pain in MS  
**Setting:** MS clinics, MS society  
**Intervention:** Reflexology  
**Comparison:** Sham

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Impact</th>
<th>Number of Participants</th>
<th>Certainty of Evidence</th>
</tr>
</thead>
</table>
| Reduction in pain assessed with: VAS, MPQ | Compared to baseline; significant decrease in median pain VAS in both reflexology (50% decrease at week 10) and sham (50% decrease at week 10) (166). Significant reduction in BPI scores in both groups, reflex group but no significant differences between groups (166). There were changes in mean pain VAS in both reflexology (pre-test 5.72, post-test 3.16, 2 months 4.64) and control (pre-test 5.88, post-test 5.60, 2 months 5.32) (169). | 110 (2 RCTs) | VERY LOW  

| Reduction in disability assessed with: BI, RMDQ | Both the intervention and sham groups showed a significant decrease in RMDQ by the end of the treatment period. BI scores in both groups remained relatively stable throughout the duration of the trial in both groups (166). | 71 (1 RCT) | VERY LOW  |

| Improvement in Quality of Life assessed with: MSIS-29 | MSIS-29 psychological sub scale improved in both intervention and sham by week 10. Physical sub scale significant decrease in both intervention and sham, however this | 71 (1 RCT) | VERY LOW  |
Reduction was greater in the treatment group by week 10 (166).

| Reduction in Fatigue assessed with: MFIS, FSS | MFIS physical sub scale score significantly improved in both sham and treatment by week 10. Significant reduction MFIS cognitive sub scale score in both sham and treatment by week 10. Significant reduction in MFIS psychological sub scale in both sham and treatment by the end of the treatment period. Both sham and treatment demonstrated a significant reduction in fatigue by week 10 (166). | 71 (1 RCT) | 
| Reduction in depression assessed with: BDI - II | Both sham and treatment groups showed a significant reduction in values by week 10 (166). | 71 (1 RCT) | 
| Reduction in Spasms assessed with: VAS for spasm | Both sham and treatment demonstrated a statistically significant decrease in spasm by the end of the treatment (166). | 71 (1 RCT) |

BPI: Brief Pain Inventory; FSS: Fatigue Severity Scale

Footnotes:
1 Downgraded two levels due to high risk of attrition bias and unclear risk of bias in blinding and allocation concealment.
2 Downgraded two levels due to high risk for imprecision (small sample size).

Table 8. Summary of findings tables for Cochrane review
A table on the summary of findings of the included studies including outcomes, impact, number of participants and level of evidence.

3.5.2. Overall Completeness and Applicability of Evidence

Despite a comprehensive search of the literature, only 10 trials evaluating a wide variety of non-pharmacological treatments fulfilled the inclusion criteria. Due to the quality of the published studies, many aspects of non-pharmacological interventions for MS pain remain unproven. Further, there were only few studies (which were heterogeneous) that evaluated a given type of intervention, which did not permit pooling data for quantitative analyses. There are other non-pharmacological interventions (e.g. yoga, massage therapy and radial shock wave therapy) which have been used for pain relief in people with MS, however, studies evaluating these interventions did not fulfil the inclusion criteria for
this review. Cost-effectiveness of the intervention and reporting of safety or adverse events for participants were not evaluated in any of the included trials. Overall, the review identified many issues relating to the studies evaluating non-pharmacological interventions in chronic pain in MS; which could affect the overall completeness and applicability of evidence. The gaps in the evidence base for non-pharmacological management of chronic pain in people with MS include the following.

- Limited and/or lack of high-quality evidence for the effectiveness of non-pharmacological interventions.
- Complexity and different mechanisms related to chronic pain in MS.
- Broad range of non-pharmacological interventions used in different context and with scope.
- Difficulty of blinding and incorporation of a control or placebo (sham).
- Lack of use of Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations for measures of significance and standardised measurement outcomes.
- Difficulty with knowing the effective dose or duration for many non-pharmacological interventions due to lack of definitive mechanisms.

Non-pharmacological interventions are therapist- and operator-dependent and may be prone to multiple combined mechanisms or 'bundled effects' (193). Suggestions for future improvements in quality of evidence include robust studies emphasising on the mechanisms of pain in MS.

3.5.3. Quality of the Evidence

All 10 included studies were rated as 'very low' quality for methodological evidence due to risk of bias and flaws in their methodological design.

- Underpowered from low sample size and lack of study power calculation.
- Lack of reporting in IMMPACT suggestion of > 30% or 50% change in pain scores for clinical significance.
- Limited reporting of complete data.
- Unclear in the reporting of study authors’ conflicts of interest, funding sources (171, 172)
- Difficulty controlling for therapist-dependent bias, patient motivation and activity/interventions outside of treatment.

In summary, these limitations affected the quality of the evidence and highlights the importance of good methodological practices in research. This is especially important given the difficulty in recruitment of targeted study cohorts (with adequate sample sizes) and difficulties associated with controlling for patients’ personal and other confounding factors such as, patient motivation and self-efficacy, comorbidity and activity level outside of therapy programmes), which influence compliance and delivery of therapy, thus impacting on outcomes. A summary of quality of evidence and risk of bias is represented in Figure 13.
Figure 13. Risk of bias diagrams for Cochrane review
A graphical representation of the risk of bias of the included studies in 2 graphical forms.
3.5.4. Potential Biases in the Review Process

The review authors followed a number of steps to ensure the reduction of bias in the review process. First, the review authors independently reviewed and assessed all articles. Second, the review authors adhered strictly to the inclusion and exclusion criteria for the studies and extraction and interpretation of the data, and followed the GRADE handbook. However, a number of limitations in the methodological quality of the review itself, and the completeness of the retrieved literature, cannot be ruled out. Despite the extended range of terms that were used to capture the widest possible selection of the relevant literature, we were not able to rule out some degree of selection bias from the literature search (194). Possibility of publication bias cannot be omitted as we were not able to include negative trials or other trials which are yet to be published in academic literature (162). Further, reference bias (195) is a further possibility, as we searched only reference lists within the relevant papers for additional articles. We welcome contact from any readers who are aware of important high-quality studies which are not included in this review.

3.5.5. Agreements and Disagreements with Other Studies or Reviews

There are limited systematic reviews in the area of non-pharmacological management of chronic pain in MS. This review highlights existing evidence and gaps in the literature. There are some similarities which are consistent between this review and another published non-Cochrane systematic review (49). However, there are methodological differences of this review and the review by Jawar et al (49). Specifically inclusion of only high-quality studies (randomised controlled trials (RCTs) and clinical controlled trials (CCTs)) and use of standardised tools - the Cochrane Handbook for Systematic Reviews of Interventions (161) and the ‘GRADE’ for the methodology and interpretation of findings. We think this review addressed the methodological issues in systematically reviewing the evidence for the management of chronic pain in people with MS (193). This is reflected in the findings of various issues within the included studies in this review, included blinding, small sample sizes, determination of the right dose/duration of treatment and focus on other outcome measures other than pain intensity such as adverse effects and patient compliance and adherence to therapy.

3.6. Authors’ Conclusions

The conclusions and summary of the review will be discussed.

3.6.1. Implications for Practice

Despite use of a range of non-pharmacological interventions for the treatment of chronic pain in people with multiple sclerosis, this review found 'very low-level' evidence for the use of such interventions. Therefore, it is difficult to recommend routine use of non-pharmacological interventions alone for the treatment of chronic pain in an MS population. However, findings suggest that use of non-pharmacological intervention in combination with pharmacological agents is reasonable. The findings of this review also highlight the existing gaps in the literature and emphasise the need for robust evidence to support these modalities. Clinician involvement is vital to build evidence from everyday clinical practice. The clinical applicability of findings of this review need to be confirmed in future studies with robust study design, larger sample sizes and long-term follow-up.
3.6.2. Implications for Research

This review shows that there are significant gaps in the literature on non-pharmacological management of chronic pain in MS. Future research implications include the following.

- Robust studies with reduced risk of bias, with adequate allocation, randomisation procedures
- Standard reporting of pain as defined by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) (103)
- Reporting pain measures desired by patients (196)
- Appropriate and careful selection of study cohort and larger sample size
- Emphasise on details of pain mechanism, localisation pattern, severity and impact on everyday function
- Impact and burden on carer and family, or both
- Intervention-related adverse effects/complications
- Long-term impact of interventions
- Cost associated with the interventions

3.7. Summary of Chapter

Non-pharmacological therapies are widely used, both in hospital and ambulatory/mobility settings to improve pain control, coping ability, daily function and QoL. Examples of common therapies include multidisciplinary rehabilitation management, psychological interventions, TENS and tDCS (49). Specific questions addressed in this review included “Are non-pharmacological interventions (unidisciplinary and/or multidisciplinary rehabilitation) effective in reducing chronic pain in people with MS?” and “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 people with MS?” All published RCTs, including cross-over studies, and CCTs that compared non-pharmacological therapies with a control situation for managing chronic pain in people with MS were included. We included trials if the study population had a confirmed diagnosis of MS, aged 18 years and older with chronic pain and minimum levels of pain on VAS of 3/10.

The primary outcome was determined by validated measures which produced a reduction in pain. Due to the multidimensional model of pain, we included secondary outcomes which focused on quality of life, depression and anxiety and functional impact scores. Two review authors independently assessed the methodological quality of the included studies using the ‘Risk of bias’ tool outlined in the Cochrane Handbook for Systematic Reviews of Interventions (161). All quantitative data was entered and analysed in the RevMan software (Review Manager 2014). The results of individual studies were discussed and presented in table and graphical format, where data aggregation was not possible. We assessed the quality of the body of evidence using the GRADE Working Group approach as outlined in the GRADE handbook (161).

Overall, 10 RCTs with 565 participants fulfilled the inclusion criteria of this review, which evaluated various non-pharmacological interventions for the management of chronic pain in people with MS, which included: physical therapy (Ai chi water exercise), psychotherapy (telephone self-management, cognitive restructuring, neurofeedback and hypnosis), neuromodulatory techniques (tDCS, tRNS), reflexology and TENS. The included trials were heterogeneous in terms of type and intensity of interventions evaluated and outcome measures used. The study quality varied and formulating pooled
evidence was limited due to high risk of bias, underpowered studies (small sample size) and lack of data on changes of pain outcomes in majority of the studies.

In summary, TENS reduced pain scores for lower back pain; Ai Chi Water exercises reduced pain intensity and improvements in spasm, QoL and fatigue; tDCS reduced pain intensity but not in fatigue and anxiety and depression; tRNS improved pain scores, depression or anxiety and fatigue; telephone-delivered self-management program reduced pain intensity, catastrophisation, improvement in self-efficacy, fatigue and QoL; EEG biofeedback reduced pain intensity, fatigue and pain interference; and reflexology reduced pain intensity, disability, fatigue, psychological and physical impact and depression. The gaps in the evidence base for non-pharmacological management of chronic pain in people with MS include limited and/or lack of high-quality evidence, complexity and different mechanisms related to chronic pain in MS, broad range of non-pharmacological interventions used in different contexts, difficulty of blinding and incorporation of a control or placebo (sham); lack of use of IMMPACT recommendations for measures of significance and standardised measurement outcomes and difficulty with knowing the effective dose or duration for many non-pharmacological interventions.

Despite use of a range of non-pharmacological interventions for the treatment of chronic pain in people with MS, this review found ‘very low level’ evidence for the use of such interventions. The clinical applicability of findings of this review need to be confirmed in future studies with robust study design, larger sample sizes and long-term follow-up.

3.8. Conclusion

This chapter presents an up-to-date summary of the current literature on non-pharmacological management of chronic pain in MS. This chapter highlighted the ‘very low quality’ of evidence and the gaps in the literature. The next chapter will attempt to address some gaps in the literature and help with the ‘development’ of the thesis as highlighted in Chapter 2. Chapter 4 will focus on changes over-time for patients with chronic and MS in the community and address issues such as pain characteristics, healthcare utilisation and carer stress.
Chapter 4. Chronic Pain in Multiple Sclerosis: a 10-year Longitudinal Study

4.1. Introduction

There is a high prevalence of chronic pain in MS which tends to increase over time. To date there is a lack of longitudinal data on chronic pain in MS past seven years (8, 9) and more research is needed to inform clinical practice in regards to MS-related pain and its long-term impact on disability, functional activity, carer stress and environmental factors (such as living arrangements) (9, 197, 198). A longitudinal 7-year follow-up study conducted in a community cohort showed that though average pain intensity rating did not change over time (at seven years from baseline), more participants reported higher rates of pain and greater disability limiting their daily activities. Further, there was deterioration in the quality of life and increased dependency due to pain-related disability. The authors also found that participants were using less pharmacological medications and using other non-conventional therapies, which is mainly due to barriers to access to healthcare services, lack of finances and fear of side effects (9). A study by Ehde et al reported a high prevalence of chronic pain and increased pain-related disability (44%) in a community cohort of MS (199). Stenager E et al in another 5-year longitudinal study found a significant increase in the number of chronic and acute pain syndromes since diagnosis overtime with deterioration in disability (8).

The objective of this study was to examine longer-term effects of chronic pain over ten years in MS in the community and assess the pain-related disability, carer burden, healthcare utilisation and management strategies.

4.2. Methods

4.2.1. Setting

This was a prospective longitudinal study conducted at the Rehabilitation Department of Royal Melbourne Hospital (RMH), a tertiary referral hospital in Victoria and Australia. The source of participants was from the RMH MS database and contains detailed MS patient information including demographic data, diagnosis details (using McDonald’s criteria (200)), pain characteristics, pain severity and management. This study was approved by the Melbourne Health Human Research and Ethics Committee (HREC 2016.021). The profile of patients captured by the RMH MS database is described elsewhere (9, 120). A pilot evaluation of pain outcomes of persons with MS at the RMH was published in 2005 (n =101), and further 7-year follow up study of this cohort (n = 74) for long-term outcomes was published in 2013 (9).
4.2.2. Participants
The participants for the present study were recruited from an initial cohort of MS participants from the RMH MS Database in 2005 (n = 101) (120). The inclusion criteria for the study were: > 18 years of age, fulfilled McDonald’s diagnostic criteria (200, 201) and had chronic pain defined as (constant or intermittent) pain experienced every day for greater than or equal to three months in the six months before the interview (8).

The exclusion criteria included: participants with significant co-morbidities (medical instability due to brittle diabetes or angina) or unstable psychiatric disorders, patients with acute pain and/or who did not fulfil the criterion of chronic pain.

Caregiver for this study was defined as ‘a person who lives with the participant with MS and provides them with the most care and assistance’ (202-204).

4.2.3. Procedure
All eligible patients in the database who participated in the longitudinal study in 2013 were contacted by phone, invited to participate in this study and were then assessed by an independent assessor. A face-to-face structured interview technique was used, which was conducted by an independent trained research officer using a structured format and standardised instruments (see Measures). All interviews took approximately 45 minutes and were based in the community setting and home visits. The assessor did not provide prompts but did assist those who had difficulty answering the questionnaire. Appropriate rest breaks were also provided during these interview sessions. All assessments were secured and entered into the database by an independent data entry officer.

4.2.4. Measurements
All measurement tools used in the baseline and 7-year follow-up study in 2013 were used for this study. These included pain assessment by using temporal criteria (chronic) as well as a symptom-orientated approach using a structured questionnaire and interview (9). All reported pain that fulfilled the study criteria was included, incorporating neuropathic and nociceptive types (19, 205, 206).

4.2.4.1. Multiple Sclerosis-Related Measures
MS-related information collected included the participant demographic details and information about MS symptom onset and diagnosis obtained from the RMH Rehabilitation database.

4.2.4.2. Pain Measures
These included in the last six months: location of pain, descriptive pain intensity, duration of pain (in years), temporal aspects of pain and trigger factors. Types of pain were categorised to neuropathic pain (characterised by burning, numbness, itching, pricking, allodynia and hyperalgesia) and nociceptive pain (characterised by aching, dull, stabbing, throbbing, squeezing, cramping and pain on movement) by descriptors. Participants could have characteristics of neuropathic and nociceptive
pain. Other types of pain included trigeminal neuralgia, painful spasms and back pain and headache to be consistent with previous a 7-year longitudinal study (9).

Information in regards to pharmacological pain treatments was collected by listing the medications used (current and past six months) and classified using categories from the monthly index of medical specialities Australia (207). The participants were also asked about their usual pain management across the categories of medication, physical/mechanical/temperature manipulation, rest/sleep exercise, distraction or alternative techniques. Other information on perceived barriers and access to healthcare services (medical practitioners, allied health and alternative health practitioners) in the last 12 months were also collected (208).

4.2.4.3. Visual Analogue Scale (VAS)

The VAS, a unidimensional measurement of pain intensity across a continuum of values, was used to assess the pain intensity. It is quick and easy to administer and widely used in adult populations. It was asked on average relating to the last six months as was used in the previous 7-year follow-up study (9).

4.2.4.4. Simple Descriptive Pain Scale

The simple descriptive pain scale, a unidimensional measurement tool, was used to measure the severity of pain by descriptors (no pain, mild pain, moderate pain, severe pain, very severe pain and worst possible pain) (79).

4.2.4.5. Chronic Pain Grade (CPG)

The CPG, a multidimensional measure, evaluated two dimensions of chronic pain: pain intensity and pain-related disability. These sub-scores were combined to calculate a CPG from 0 (no pain) Grade I (low disability–low intensity), Grade II (low disability–high intensity), Grade III (high disability–moderately limiting), and Grade IV (high disability–severely limiting) (206).

4.2.4.6. The Assessment of Quality of Life (AQoL)

The AQoL was used to assess health-related quality of life in four domains: independent living, social relationships, physical senses and psychological well-being. AQoL has been validated in a range of patient groups (209).

4.2.4.7. Carer Strain Index (CSI)

The CSI is a 13-item tool that describes stressful aspects of caregiving. The caregiver indicated how stressful each identified item was through ‘yes’ and ‘no’ responses; a score of ≥7 out of 13 indicates caregiver stress (202, 203).
4.3. Data Analysis

All analyses performed were consistent with the procedures adopted in the previous baseline and 7-year follow-up study. Descriptive statistics described the prevalence and characteristics of pain, utilisation of health care, perceived barriers to treatment and pain management techniques and carer strain.

Due to the small group size and the skewed distribution, non-parametric statistical analyses (Kruskal Wallis test) was used to compare patients through various CPG. The AQoL utility scores were calculated according to published guidelines, and the Wilcoxon signed-rank test was used to compare AQoL scores between the 7-year and 10-year follow-ups. All calculations were performed using IBM SPSS for Windows version 22.0, and statistical significance was determined by a level of <0.05.

4.4. Results

Of the 74 participants assessed to have chronic pain based on the aforementioned definition, 70 participants were recruited for this 10-year longitudinal study. Four participants were unable to be contacted. The recruitment process is shown in Figure 14.

![Flowchart of recruitment process]

*Figure 14. Recruitment process for 10-year longitudinal study
Flowchart of recruitment process*
The mean age of the participants was 59.8±9 years (range 39-74 years) and the majority (70%) were female. Mean disease duration since MS diagnosis was 19.5 years (range = 15-25 years), and all participants had the progressive MS type which is expected given the participant’s disease duration. At 10-year follow-up, 31 (44%) participants were either living with a private carer, a family member who is a carer or in a high-care (nursing home) facility, whereas every participant was still living at home at 7-year follow-up (Table 9).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>7 year follow up n=(% (unless stated different)</th>
<th>10 year follow up n=(% (unless stated different)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) [mean (SD), range]</td>
<td>55.3 (8.7) 35-71</td>
<td>59.8 (9), 39-74</td>
</tr>
<tr>
<td>Sex female</td>
<td>53 (71.6)</td>
<td>49 (70)</td>
</tr>
<tr>
<td>Living Alone</td>
<td>21 (28.4)</td>
<td>10 (11.6)</td>
</tr>
<tr>
<td>Partner/Family</td>
<td>53 (71.6)</td>
<td>29 (34.9)</td>
</tr>
<tr>
<td>Carer(Private,family,Institution)</td>
<td>-</td>
<td>31 (44.2)</td>
</tr>
<tr>
<td>Disease Duration</td>
<td>16.5 (12-22)</td>
<td>19.5 (15-25)</td>
</tr>
<tr>
<td>MS type</td>
<td>19 (25.7)</td>
<td>0</td>
</tr>
<tr>
<td>Relapsing remitting</td>
<td>46(62.2)</td>
<td>61(87)</td>
</tr>
<tr>
<td>Secondary progressive</td>
<td>9(12.2)</td>
<td>9(13)</td>
</tr>
</tbody>
</table>

Table 9. Socio-demographic characteristics of participants for 10-year longitudinal study
A summary of patient characteristics compared between 7-year and 10-year studies.

4.4.1. Pain Measures

The pain measures reported by the participants were similar to those at the 7-year follow-up except there was a greater representation of bilateral pain locations (limb, trunk and facial pain) compared to baseline and 7-year follow-up (Table 10). There was an increase in the number of participants reporting 'worst pain possible' for pain intensity, 12(13.9%) compared to 1(1.6%) at baseline and 2(1.6%) at 7-year follow-up. The most common location of pain reported was bilateral lower limbs 45(64.2%) and the most commonly described descriptive pain intensity were mild 23 (26.7%). VAS, temporal aspect of pain, pain descriptions and duration were similar.

At 10-year follow-up, more participants used medications compared to 7-year follow-up. There was an increase in the number of participants using non-opioids, opioids, muscle relaxants, anticonvulsants and antidepressants (except anti-inflammatories) but not to the extent at baseline (Table 11). The most common analgesics used were non-opioids 31 (44.2%), and the most common non-pharmacological intervention was physical/electrical 45 (64.3%) which included massage, hydrotherapy, change in position and transcutaneous electrical nerve stimulation. There was a similar use of non-pharmacological interventions in the 10-year follow-up compared to 7-year follow-up.
4.4.2. Healthcare Utilisation

There was an increase in the use of health professionals at the 10-year follow-up. The two main practitioners were general practitioners and neurologists [61 (87.1%) and 60 (85.7%) respectively] compared to 40 (54.1%) and 46 (62.2%) respectively at the 7-year follow-up. However, there were still few participants utilising rehabilitation and pain specialists. There were more participants reporting side-effects 5 (7.1%) and being fearful of taking medications 10(14.3%); these were considered barriers to accessing pharmacological treatments. Other barriers, such as environmental and cognitive barriers were similar at the two time-points.

### Table 10. Characteristics of chronic pain in 10-year longitudinal study

<table>
<thead>
<tr>
<th>Location</th>
<th>Baseline (n=61)</th>
<th>7 year follow up (n=74) n (%)</th>
<th>10 year follow up (n=70) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head-Unilateral</td>
<td>7 (11.5)</td>
<td>8 (10.8)</td>
<td>8 (4.2)</td>
</tr>
<tr>
<td>Head-Bilateral</td>
<td>10 (16.4)</td>
<td>12 (16.4)</td>
<td>20 (28.5)</td>
</tr>
<tr>
<td>Limbs-Upper unilateral</td>
<td>13 (21.3)</td>
<td>18 (24.3)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Limbs-Upper bilateral</td>
<td>8 (13.1)</td>
<td>7 (9.5)</td>
<td>18 (25.7)</td>
</tr>
<tr>
<td>Limbs-Lower unilateral</td>
<td>11 (18)</td>
<td>13 (17.6)</td>
<td>7 (10)</td>
</tr>
<tr>
<td>Limbs-Lower bilateral</td>
<td>26 (42.6)</td>
<td>39 (52.7)</td>
<td>45 (64.2)</td>
</tr>
<tr>
<td>Trunk unilateral</td>
<td>8 (13.1)</td>
<td>12 (16.2)</td>
<td>2 (28)</td>
</tr>
<tr>
<td>Trunk bilateral</td>
<td>20 (32.8)</td>
<td>16 (21.6)</td>
<td>28 (40)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Descriptive pain intensity</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>17 (27.9)</td>
<td>24 (32.4)</td>
<td>23 (26.7)</td>
</tr>
<tr>
<td>Moderate</td>
<td>33 (54.1)</td>
<td>29 (39.2)</td>
<td>16 (18.6)</td>
</tr>
<tr>
<td>Severe</td>
<td>5 (8.2)</td>
<td>16 (21.6)</td>
<td>17 (19.7)</td>
</tr>
<tr>
<td>Very Severe</td>
<td>2 (3.3)</td>
<td>3 (4.1)</td>
<td>2 (2.3)</td>
</tr>
<tr>
<td>Worst Pain possible</td>
<td>1 (1.6)</td>
<td>2 (1.6)</td>
<td>12 (13.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Types of Pain</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysesthetic</td>
<td>37 (60.7)</td>
<td>36 (48.6)</td>
<td>38 (54.2)</td>
</tr>
<tr>
<td>Nociceptive</td>
<td>4 (6.6)</td>
<td>6 (87.8)</td>
<td>60 (85.7)</td>
</tr>
<tr>
<td>Trigeminal Neuralgia</td>
<td>4 (6.6)</td>
<td>8 (10.8)</td>
<td>7 (10)</td>
</tr>
<tr>
<td>Painful spasms and Back pain</td>
<td>33 (54.1)</td>
<td>27 (36.5)</td>
<td>28 (40)</td>
</tr>
<tr>
<td>Headache</td>
<td>13 (21.3)</td>
<td>7 (9.5)</td>
<td>7 (10)</td>
</tr>
</tbody>
</table>

| VAS (mean)                        | 5.3            | 5.2                          | 5.2                           |
4.4.3. Quality of Life Measures

At the 10-year follow up QoL of the participants deteriorated significantly, particularly in the following domains: illness (p = 0.001), independent living (p < 0.001), social relationships (p = 0.001) and physical senses (p <0.001). This suggests that participants were now more dependent. Interestingly, there were no statistically significant changes in the psychological well-being domain, suggesting that many had adapted to the lifestyle and circumstances. The CSI mean was 5.4 but in 6/13 cases the CSI score was 7 or higher which represented significant carer stress either through pain or other MS-related symptoms (204).

4.4.4. Chronic Pain Grade

The CPG classified chronic pain severity, based on scores for items on pain intensity and pain-related disability. There were similar scores on the CPG between the 10-year and 7-year-follow up periods, but more participants had progressed to higher CPG III 7(10%) and CPG IV 14(20%) suggesting greater pain-related disability (Table 5).

4.5. Discussion

This prospective longitudinal study showed that in a 10-year time-period, 70 participants had chronic pain. A significant proportion of participants had developed greater bilateral body pain involving the trunk and limbs. However, there were no greater pain types compared to 7-year follow-up, and there was greater reporting of pain as ‘worse as it could be’ over time. This suggests that although the mean pain score remains the same as previous time points, there were now more people describing greater pain subjectively suggesting a greater emotional component to their chronic pain. These findings were different from the 5-year longitudinal study where there was an increase in chronic pain syndromes. However, there were methodological differences including the listing of specific pain locations, the use of acute and chronic syndromes and neuropathic and nociceptive definitions (8).
Types of pain, mean pain scores and pain descriptors remained similar throughout the time periods. The similarity in mean pain scores over time could be explained by a phenomenon known as ‘response shift’ (210, 211). This phenomenon is a re-conceptualisation of the impact of chronic disease over time, and these changes reflect the adaptation or accommodation for an illness or chronic condition and should be taken into consideration for longitudinal studies (210, 211). This has implications for measurement properties and outcome measures (204). Given that there is a high prevalence of chronic pain in neurological conditions, neurologists still rank treating chronic pain as low (201). However, in this study, the most common health professionals involved in their care were neurologists and general practitioners, but there was limited consultation with pain and rehabilitation specialists.

This study cannot comment on the development of widespread pain as the previous 7-year longitudinal study did not define this term. Widespread pain is defined in the literature as pain on the left side of the body, right side of the body, above the waist, below the waist and axial skeleton (212). There is limited evidence on the pathophysiology of chronic pain and the development of widespread pain in MS which is based on other chronic pain states (16). However, previous studies have shown that individuals with chronic pain disorders can go on to develop widespread chronic pain (213, 214). Postulated mechanisms include central sensitisation which can develop in individuals from a repetitive nociceptive source that produces an expansion of receptive fields and hyperalgesia (11, 214). Fibromyalgia-type symptoms were also common in MS patients and higher than the general population. An explanation is sharing the female sex as a risk factor which is common in both conditions. Central sensitisation mechanisms include long-term potentiation, altered descending inhibitory systems and a change in signalling pathways and synaptic plasticity (215, 216). Other mechanisms of ongoing pain include ongoing nociception from spasticity, posture and neuropathic mechanisms which include deafferentation and upregulation in neuroinflammation in the dorsal root ganglion (6, 65, 217).

Treatment of chronic pain in MS is difficult, and there is a paucity of evidence for the effectiveness of pharmacological and non-pharmacological treatments. Common pharmacological treatments include tricyclic antidepressants and gabapentinoids (218), but there is a lack of evidence for non-pharmacological treatments which may be important for future therapy, as barriers to treatment include fear of taking medications and side-effects (9, 201). Despite these barriers to pharmacological treatment, participants used more medications over time in this study. This phenomenon could be explained by ongoing prescription by medical practitioners, highlighting the importance of reviewing medications for their effectiveness and cessation of medications that do not benefit. This study highlights the need for increased awareness of medication safety, polypharmacy and prescribing errors, supported by a literature review of medication safety in Australia (219).

As expected there was a progression of the disease and to more severe pain grade with deterioration in AQOL scores. This deterioration was manifested clinically by increased dependence and greater pain-related disability and was associated with a significant percentage of participants who now required care from another individual, carer or institution 31(44%). Caregivers are vital in maintaining people with MS in the community and caregiver strain is associated with increased caregiver burden and decreased quality of life (202, 204). Although only participants identified as having a carer, more than half of the carers complained of sleep disturbance, inconvenience, physical strains, family and personal constraints. The results of this study were similar to other reports with demands on personal plan, emotional adjustments and sleep disturbance (203, 204).
The strengths of this longitudinal follow-up study include retention of a large proportion of the original participants, ensuring a definitive diagnosis of MS, standardised definition of pain and collection of information through face-to-face interviews. The limitations of the study include small sample size and potential sampling bias, although participant demographics were similar to other MS prevalence studies (9, 16). Other limitations include not having a control group and all findings being correlational and probably not fully representing the impact of chronic pain due to other factors in daily activities and psychology. Given this cohort was associated with only a single site, these findings may not be generalised to all MS patients in the community. MS patients with no pain were not included in the study, as this was a criteria in the 7-year follow-up study, which did not allow for a comparison with those with no pain and due to the length of time of MS diagnosis, only secondary progressive and primary progressive MS types were involved. The use of descriptors for classifying neuropathic and nociceptive pain types is another limitation of the study as participants may have descriptors representative of both types. Use of the term mixed pain relating to different pains through different pathophysiological mechanisms that have nociceptive and neuropathic components (11) may be more beneficial. However, in order to be consistent and for comparison with the previous 7-year follow-up longitudinal study this classification system was retained (9). Unlike the previous study, this longitudinal study included participants residing in institutions, which may result in an over-representation of pain and disability compared to the previous study. However, these participants were also present in 7-year follow-up, and it is important to note their progression to institutions, increased care needs and costs. Although this study did not include the Expanded Disability Status Scale (EDSS), the CPG was included as a measurement of assessing pain and its impact on disability. Future studies using regression analysis for EDSS and pain scores is a potential to link disability and pain.

4.7. Summary of Chapter

There is a high prevalence of chronic pain in MS which tends to increase over time. To date, there is a lack of longitudinal data on chronic pain in MS past seven years (9). This was a prospective longitudinal study conducted at the Rehabilitation Department of RMH, and the source of participants was from the RMH MS database. This study was approved by the Melbourne Health Human Research and Ethics Committee (HREC 2016.021).

The participants for the study were recruited from an initial cohort of MS participants from the RMH MS Database in 2005 (n = 101). The inclusion criteria for the study were: > 18 years of age, fulfilled McDonald’s diagnostic criteria and had chronic pain defined as (constant or intermittent) pain experienced every day for greater than or equal to 3 months in the six months before the interview. All eligible patients in the database who participated in the longitudinal study in 2013 were contacted by phone, invited to participate in this study and were then assessed by an independent assessor. A face-to-face structured interview technique was used.

All measurement tools used in the baseline and 7-year follow-up study in 2013 were used for this study. These included pain assessment by using temporal criteria (chronic) as well as a symptom-oriented approach using a structured questionnaire and interview. Due to the small group size and the skewed distribution, non-parametric statistical analyses (Kruskal Wallis test) was used to compare patients through various CPG. The AQtL utility scores were calculated according to published
guidelines, and the Wilcoxon signed-rank test was used to compare AQoL scores between the 7-year and 10-year follow-ups.

This prospective longitudinal study showed that in a 10-year time-period, 70 participants had chronic pain. A significant proportion of participants had developed greater bilateral body pain involving the trunk and limbs. However, there were no greater pain types compared to 7-year follow-up, and there was greater reporting of pain as ‘worse as it could be’ over time. As expected there was a progression of the disease and to more severe pain grade with deterioration in AQOL scores. This deterioration was manifested clinically by increased dependence and greater pain-related disability and was associated with a significant percentage of participants who now required care from another individual, carer or institution 31(44%).

4.8. Conclusion

This study shows that there is an increased need to be aware of chronic pain in MS and treatment is difficult despite the use of multiple treatment modalities as pain quality, intensity and location changes over time. Physicians should be encouraged to consider pain and treat pain given its potential to cause limitation in activity, lower quality of life and increase carer stress and burden. Current practices for management of chronic pain include a pain management program or interdisciplinary management. The next chapter evaluates this current practice and makes further recommendations.
Chapter 5. Interdisciplinary management for chronic pain in central nervous system disorders: A retrospective study

5.1. Introduction

Other than MS, other common central nervous system disorders associated with central pain include stroke, Parkinson's disease (PD) and spinal cord injury (SCI). Pain is a common complaint in these conditions with studies showing 40-75% of people with Parkinson’s disease, 70-80% of people with spinal cord injuries and 70% of people with stroke complain of pain. Similarly to people with MS, there is little evidence regarding pharmacological and non-pharmacological treatments.

The current understanding of chronic pain management emphasises a patient-centred, goal-focused and interdisciplinary approach. As central nervous system disorders are associated with a wide range of symptoms, interdisciplinary interventions should be beneficial in the management of pain and disability for those with these conditions (99, 220). There has been only one study which examined the efficacy of interdisciplinary management specifically in MS for chronic pain (99). This was a retrospective study which examined the outcomes of 20 participants with MS who entered an outpatient chronic pain rehabilitation program compared to those people without MS. It was concluded that participants with MS had significant changes in pain intensity, depression and daily functioning following treatment, similar to people without MS. This study found that participants with MS can participate in existing interdisciplinary interventions for pain and should be offered this treatment option (99).

This study aims to compare the findings of this previous study in a larger group of patients, and in numerous pain management services throughout Australasia. The source of the data for this study is the electronic Persistent Pain Outcomes Collaboration (ePPOC), a clinical outcomes registry developed in Australia to assess outcomes of people referred to pain management services. ePPOC collects data using standardised assessment tools, with the aim of establishing benchmarks to drive treatment efficacy and quality improvement. Data collection started in 2013 with eight participating centres in Australia and now involves 57 centres in Australia and New Zealand, with support from specialist societies and consumer organisations. Currently, ePPOC is implemented by individual sites and employ their staff to enter data and collection of information was voluntarily by patients. A recent study described the establishment of the registry, and its potential to improve outcomes for those experiencing chronic pain and for research purposes (221). The hypothesis was that people with central nervous system disorders and chronic pain would also benefit from a pain management program, with a reduction in catastrophizing and improvement in self-efficacy.

5.2. Methods
5.2.1. Objective
The objective of this study was to compare pain outcome measures of people with a central nervous system disorder with those without these conditions after an outpatient interdisciplinary-based treatment. The central nervous system disorder groups were made up of people with either MS, stroke, PD or SCI as they were the most common neurological comorbidity in this pain database. This study will outline methods used for interpretation of a new clinical database involving an Australian and New Zealand cohort.

5.2.2. Design
This study was a retrospective cohort study based on data from the ePPOC registry. The ePPOC registry contains data from initial, review and end of episode questionnaires (i.e. discharge or primary pain treatment completion). These questionnaires include questions relating to patient demographics (gender, date of birth, work status, health care utilisation, and medication use) and comorbidities. Also included were standardised, validated pain-related assessment tools. Ethics was approved by the Melbourne Health Human Research and Ethics Committee (HREC 2017.073).

5.2.3. Population
The inclusion criteria for the study included participants who were attending a participating pain management service, aged 18 years or older.

5.2.4. Procedure
Permission was obtained from the ePPOC Data Access Working Group to access patient-reported outcomes and registry information. All patient and facility data were de-identified for confidentiality. Two independent reviewers and a statistician reviewed and collated the data, and the results were reviewed by the other authors involved in the study. The focus of the study was the comparison of outcome data for people with and without a central nervous system disorder who had completed interdisciplinary interventions (e.g. individual appointments, pain program groups, pain education groups, physiotherapy, occupational therapy, psychology and/or procedures/interventions).

5.2.5. Outcome Measures
The information collected under ePPOC included demographic and clinical information, such as physical measurements, healthcare utilisation and medication use. The standardised assessment tools included in the ePPOC questionnaires included:

5.2.5.1. Brief Pain Inventory
The Brief Pain Inventory (BPI) is an 11-item self-administered questionnaire used to evaluate the severity of a patient's pain and impact on the ability to undertake a range of activities. The BPI provides two scores describing pain severity and pain interference. (222).

5.2.5.2. Depression Anxiety Stress Scale (DASS 21)
The DASS 21 is a 21 item self-reported questionnaire to measure the symptoms and the severity of depression, anxiety and stress. Scoring for each domain classifies each person from normal to extremely severe (223).
5.2.5.3. Patient Self-Efficacy Questionnaire (PSEQ)

The PSEQ is a 10-item questionnaire which assesses the confidence that people have in performing activities despite the pain they are experiencing. Higher scores are associated with stronger self-belief traits (224).

5.2.5.4. Pain Catastrophizing Scale (PCS)

The PCS is a 13-item questionnaire which assesses catastrophic thinking concerning a person's pain experience by measuring three sub-categories of rumination, magnification, and helplessness (225).

5.3. Statistical Methods

Data on patient demographics, health utilization and disease were presented descriptively. Statistical Analysis Software (SAS v9.4) was used to calculate mean values and percentages on BPI, DASS 21, PSEQ and PCS. The two-sample t-test (assuming unequal variances) was used to determine the significance of the difference between the groups. Statistical significance was defined as p<0.05.

5.4. Results

There were a total of 40,672 patients in the ePPOC registry at the time of data analysis. Of these patients, 1924 (4.7%) indicated that they had a central nervous system disorder. A comparison of the characteristics of these patients at referral is shown in Table 12. The results show that patients with central nervous system disorders tended to be older and less likely to be employed full or part-time. A higher proportion had their pain for more than 5 years and was more likely to have pain in the head, face or neck compared to patients without a central nervous system disorder.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Central nervous system disorders¹ (n = 1924) (%)</th>
<th>Without Central nervous system disorders (n = 38748) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (Median)</td>
<td>56</td>
<td>51</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>59.7</td>
<td>57.3</td>
</tr>
<tr>
<td>Male</td>
<td>40.3</td>
<td>42.7</td>
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<tr>
<td>Healthcare Utilisation²</td>
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</tr>
<tr>
<td>0 times</td>
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<td>1.9</td>
</tr>
<tr>
<td>1-4 times</td>
<td>18.8</td>
<td>21.1</td>
</tr>
<tr>
<td>5 – 10 times</td>
<td>33.7</td>
<td>33.2</td>
</tr>
<tr>
<td>&gt;10 times</td>
<td>45.5</td>
<td>43.8</td>
</tr>
<tr>
<td>Employment</td>
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<td></td>
</tr>
<tr>
<td>Full/part-time</td>
<td>10.0</td>
<td>20.1</td>
</tr>
<tr>
<td>Unemployed due to pain</td>
<td>31.1</td>
<td>34.7</td>
</tr>
<tr>
<td>Unemployed (not pain related)</td>
<td>6.2</td>
<td>5.2</td>
</tr>
<tr>
<td>Other (e.g. retired, home)</td>
<td>61.7</td>
<td>49.8</td>
</tr>
<tr>
<td>Main Pain Location</td>
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<td>13.0</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>------</td>
<td>------</td>
</tr>
<tr>
<td>Head/face/neck</td>
<td>21.0</td>
<td>13.0</td>
</tr>
<tr>
<td>Upper limb (shoulder, arm)</td>
<td>12.0</td>
<td>13.0</td>
</tr>
<tr>
<td>Lower Limb</td>
<td>12.0</td>
<td>11.7</td>
</tr>
<tr>
<td>Trunk (chest, back, abdo, hip)</td>
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<td>10.6</td>
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<tr>
<td>&lt;3 months</td>
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<tr>
<td>3 – 12 months</td>
<td>11.7</td>
<td>10.6</td>
<td>11.7</td>
<td>10.6</td>
</tr>
<tr>
<td>12 months to 5 years</td>
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<td>39.4</td>
<td>34.2</td>
<td>39.4</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>52.6</td>
<td>42.7</td>
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</tr>
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</table>

<table>
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<tr>
<th>Number of medication classes³</th>
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<tbody>
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<td>14.4</td>
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<td>3.2</td>
<td>6.1</td>
<td>3.2</td>
</tr>
</tbody>
</table>

Table 12: Patient demographics for retrospective study

Legend:
¹Central nervous system disorders included those with multiple sclerosis, stroke, parkinsons disease, traumatic brain injury and spinal cord injury
²Healthcare utilization is the total number of times a patient had seen a medical practitioner, specialist or allied health professional, or had an emergency hospital presentation, hospital inpatient admission or diagnostic test in the last three months.
³Number of medication classes was a total of the number of major drug classes the patient was using (opioids, paracetamol, anti-inflammatories, antidepressants, anticonvulsants and benzodiazepines).

Of the 1924 patients who reported central nervous system disorders, 146 (7.6%) had completed their episode of care and had returned an episode end questionnaire. Of the patients who did not report central nervous system disorders, 4281 (11.0%) had completed their episode and questionnaire. Across all assessment tools, both groups made statistically significant improvements from referral to the end of the episode as seen in Table 13. The average mean change was similar between the two groups but was only statistically significant for decreased PCS in the central nervous system disorder group (Table 4).
<table>
<thead>
<tr>
<th>Measurements</th>
<th>N=</th>
<th>Central nervous system disorders (Referral) (Mean)</th>
<th>Central nervous system disorders (End of Care) (Mean)</th>
<th>Standard Deviation</th>
<th>N=</th>
<th>Without Central nervous system disorders (Referral) (Mean)</th>
<th>Without Central nervous system disorders (End of care) (Mean)</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPI Pain Severity&lt;sup&gt;1&lt;/sup&gt;</td>
<td>133</td>
<td>6.4&lt;sup&gt;*&lt;/sup&gt;</td>
<td>5.3&lt;sup&gt;*&lt;/sup&gt;</td>
<td>2.07</td>
<td>4008</td>
<td>6.0&lt;sup&gt;*&lt;/sup&gt;</td>
<td>5.2&lt;sup&gt;*&lt;/sup&gt;</td>
<td>1.74</td>
</tr>
<tr>
<td>BPI Pain Interference&lt;sup&gt;1&lt;/sup&gt;</td>
<td>137</td>
<td>7.1&lt;sup&gt;*&lt;/sup&gt;</td>
<td>5.3&lt;sup&gt;*&lt;/sup&gt;</td>
<td>2.09</td>
<td>4141</td>
<td>6.8&lt;sup&gt;*&lt;/sup&gt;</td>
<td>5.3&lt;sup&gt;*&lt;/sup&gt;</td>
<td>2.25</td>
</tr>
<tr>
<td>Depression</td>
<td>136</td>
<td>20.0&lt;sup&gt;*&lt;/sup&gt;</td>
<td>14.2&lt;sup&gt;*&lt;/sup&gt;</td>
<td>10.06</td>
<td>4057</td>
<td>19.2&lt;sup&gt;*&lt;/sup&gt;</td>
<td>14.3&lt;sup&gt;*&lt;/sup&gt;</td>
<td>10.71</td>
</tr>
<tr>
<td>Anxiety</td>
<td>136</td>
<td>15.5&lt;sup&gt;*&lt;/sup&gt;</td>
<td>12.6&lt;sup&gt;*&lt;/sup&gt;</td>
<td>8.99</td>
<td>4037</td>
<td>12.8&lt;sup&gt;*&lt;/sup&gt;</td>
<td>11.0&lt;sup&gt;*&lt;/sup&gt;</td>
<td>8.60</td>
</tr>
<tr>
<td>Stress</td>
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<td>21.2&lt;sup&gt;*&lt;/sup&gt;</td>
<td>16.8&lt;sup&gt;*&lt;/sup&gt;</td>
<td>10.03</td>
<td>4035</td>
<td>20.5&lt;sup&gt;*&lt;/sup&gt;</td>
<td>16.9&lt;sup&gt;*&lt;/sup&gt;</td>
<td>10.03</td>
</tr>
<tr>
<td>PCS&lt;sup&gt;2&lt;/sup&gt;</td>
<td>136</td>
<td>28.8&lt;sup&gt;*&lt;/sup&gt;</td>
<td>18.6&lt;sup&gt;*&lt;/sup&gt;</td>
<td>11.71</td>
<td>3948</td>
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<td>19.2&lt;sup&gt;*&lt;/sup&gt;</td>
<td>11.71</td>
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<tr>
<td>PSEQ&lt;sup&gt;3&lt;/sup&gt;</td>
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<td>21.4&lt;sup&gt;*&lt;/sup&gt;</td>
<td>30.7&lt;sup&gt;*&lt;/sup&gt;</td>
<td>13.10</td>
<td>4081</td>
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<td>30.2&lt;sup&gt;*&lt;/sup&gt;</td>
<td>13.90</td>
</tr>
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</table>

Table 13: Assessment scores at referral to end of care for retrospective study

Legend:
<sup>1</sup>BPI= Brief Pain Inventory
<sup>2</sup>PCS= Pain Catastrophizing Scale
<sup>3</sup>PSEQ= Pain Self-Efficacy Questionnaire

<table>
<thead>
<tr>
<th>Pain Measurements</th>
<th>N=</th>
<th>Central nervous system disorders (Mean)</th>
<th>Without Central nervous system disorders (Mean)</th>
<th>Standard Deviation</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPI Pain Severity&lt;sup&gt;1&lt;/sup&gt;</td>
<td>137</td>
<td>-1.1</td>
<td>-0.8</td>
<td>2.07</td>
<td>0.11</td>
</tr>
<tr>
<td>BPI Pain Interference&lt;sup&gt;1&lt;/sup&gt;</td>
<td>133</td>
<td>-1.8</td>
<td>-1.5</td>
<td>2.09</td>
<td>0.11</td>
</tr>
<tr>
<td>Depression</td>
<td>136</td>
<td>-5.8</td>
<td>-4.9</td>
<td>10.06</td>
<td>0.29</td>
</tr>
<tr>
<td>Anxiety</td>
<td>136</td>
<td>-2.9</td>
<td>-1.8</td>
<td>8.99</td>
<td>0.14</td>
</tr>
<tr>
<td>Stress</td>
<td>135</td>
<td>-4.4</td>
<td>-3.6</td>
<td>10.03</td>
<td>0.38</td>
</tr>
<tr>
<td>PCS&lt;sup&gt;2&lt;/sup&gt;</td>
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<td>-10.3</td>
<td>-7.8</td>
<td>11.71</td>
<td>0.01</td>
</tr>
<tr>
<td>PSEQ&lt;sup&gt;3&lt;/sup&gt;</td>
<td>132</td>
<td>9.3</td>
<td>8.0</td>
<td>13.10</td>
<td>0.26</td>
</tr>
</tbody>
</table>

Table 14: Difference in mean changes between groups for retrospective study

Legend:
<sup>1</sup>BPI= Brief Pain Inventory
<sup>2</sup>PCS= Pain Catastrophizing Scale
<sup>3</sup>PSEQ= Pain Self-Efficacy Questionnaire
5.5. Discussion

At referral, patients in both groups were similar in terms of characteristics, with the proportion of females slightly higher for those with a central nervous system disorder (59.7%) compared with those without a central nervous system disorder (57.3%). This was unexpected as there is normally a higher prevalence of MS in females compared to males (226). However, this similarity may be explained due to the inclusion of other central nervous system disorders (227).

There was similar usage of healthcare in both groups, suggesting that both groups require a significant amount of healthcare support with ‘>10 times’ in the previous three months having the highest frequency in both groups. This outcome is similar to that of other reports on the impact of chronic pain on healthcare utilization (228). Both groups were high users of healthcare and reflect the chronicity and disabling nature of the cohorts referred to pain services in Australia.

In this study, trunk pain was the most common site for both groups. However, there were more participants in the central nervous system disorder group describing ‘pain in the head, face or neck’ compared to those without a central nervous system disorder (21% vs 13.5%). This could be explained by the high prevalence of facial pain conditions (trigeminal neuropathic pain, atypical facial pain) and headaches in central nervous system disorders (229).

The ePPOC registry shows that after engagement with interdisciplinary pain management, there was a reduction in pain severity scores, interference, mean depression, anxiety and stress in both groups at referral compared to end of an episode. There were changes in mean assessment scores between both groups but were non-significant. However, there was a significant difference in pain catastrophising between those with a central nervous system disorder (-10.3) and those without (-7.8). These results were similar to results from previous studies and systematic reviews which showed improvements in depression, anxiety, stress, pain interference, intensity scores and pain catastrophising after interdisciplinary management (99, 230, 231).

There was a greater reduction in mean change for PCS in those with a central nervous system disorder (-10.3) compared with those without (-7.8). This greater reduction in PCS for central nervous system disorders may be related to a slightly higher level of catastrophisation level at referral. Catastrophisation has been shown to be common in central nervous system disorders with significant disability and pain (227).

Studies on interdisciplinary treatments for chronic pain are limited by the wide range of treatments and the difficulty of separating treatment effects to specific components of an interdisciplinary treatment (232). Similarly, there are limitations to this study. As a retrospective study, it is prone to selection bias and there are multiple confounding factors and variables which could not have been excluded. Being self-reported, there is the potential for bias and inaccurate or incomplete records which can impact results. The strengths of this study include being the first study on central nervous system disorders and interdisciplinary management using the ePPOC registry.

5.6. Summary of Chapter

Other than MS, other common central nervous system disorders associated with central pain include stroke, Parkinson’s disease (PD) and spinal cord injury (SCI). Pain is a common complaint in these conditions with studies showing 40-75% of people with Parkinson’s disease, 70-80% of people with
spinal cord injuries and 70% of people with stroke complain of pain. The objective of this study was to examine the effectiveness of outpatient interdisciplinary-based treatment for chronic pain in people with central nervous system disorders compared to people who do not have these conditions. This was the first study to involve an Australian and New Zealand cohort and the use of the ePPOC database to explore the outcomes for people with central nervous system disorders.

This study was a retrospective cohort study based on data from the ePPOC registry. The ePPOC registry contains data from initial, review and end of episode questionnaires (i.e. discharge or primary pain treatment completion). The inclusion criteria for the study included participants who were attending a participating pain management service, aged 18 years or older. Permission was obtained from the ePPOC Data Access Working Group to access patient-reported outcomes and registry information. All patient and facility data were de-identified for confidentiality. Two independent reviewers and a statistician reviewed and collated the data, and the results were reviewed by the other authors involved in the study.

There were 40,672 patients in the ePPOC registry at the time of data extraction. Of these patients, 1924 (4.7%) indicated that they had a central nervous system disorder. Of the 1924 patients who reported a central nervous system disorder, 146 (7.6%) had completed their episode of pain management at the time of data extraction and had returned an episode end questionnaire. Of the patients who did not report a central nervous system disorder, 4281 (11.0%) had completed their episode and questionnaire. The ePPOC dataset shows that after engagement with an interdisciplinary pain management service, there was a reduction in pain severity scores and interference, mean depression, anxiety and stress in both groups at referral compared to end of an episode of care. These changes were non-significant between the groups. However, there was a significant difference in pain catastrophizing between those with a central nervous system disorder and those without after intervention.

5.7. Conclusion

This study shows that people with central nervous system disorders can benefit from interdisciplinary management and have similar results to those of those without these conditions, with potential greater improvement for pain catastrophising. This retrospective study offers an insight into interdisciplinary treatment and the use of the ePPOC registry in Australia and New Zealand.
Chapter 6. The Effect of Transcranial Direct Current Stimulation on Chronic Neuropathic Pain in Patients with Multiple Sclerosis: Randomised Controlled Trial

6.1. Introduction

Chronic neuropathic pain is a subcategory of chronic pain and is often difficult to treat with only pharmacological interventions (233). Pharmacological interventions include anticonvulsants and antidepressants and opioids but have limitations in the form of side effects such as drowsiness, nausea and vomiting, cognitive impairment and risks associated with dependence and tolerance (234). These side effects could result in insufficient dosages and increased risk of falls (49). Thus, chronic neuropathic pain remains inadequately treated and is therefore potentially a highly important therapeutic target in patients with MS.

There has been increasing literature on the neurobiology and processing of pain experience. M1, S1 and DLPFC have all been suggested to be involved in processing pain (235-238). The tDCS device is a non-invasive neurostimulation technique that utilises a constant low-intensity current (1-2mA) (235-238). The primary mechanism of action of tDCS is based on the modification of the excitability of neuronal activity in parts of the cerebral cortex for pain processing and perception (239, 240). It is applied to the scalp via electrodes to modulate cortical excitability through anodal or cathodal stimulation.

Anodal tDCS (a-tDCS) depolarises the resting membrane and cathodal tDCS causes hyperpolarization (241). A-tDCS of M1 has been shown to be a safe and effective technique to relieve neuropathic pain in other conditions such as post-stroke pain, trigeminal neuropathic pain, brachial plexus injury, spinal cord injury and peripheral nerve injury (242-245). M1 is identified by C3 and C4 of the 10/20 EEG system and the main mechanism is based on the modification of the excitability of neuronal activity in parts of the pain matrix. Mechanism of actions include affecting the GABAergic divisions of the thalamus and inhibiting the hyperactive thalamic nuclei which can help with pain on the contralateral side (235, 239, 246).

There have been previous randomised controlled trials into the effectiveness of a-tDCS for neuropathic pain in patients with MS (135, 163). Previous protocols used 2mA a-tDCS applied on M1 for 20 minutes for 3 and 5 days respectively. Both these studies showed that a-tDCS decreased pain severity scores, which were maintained up to 1 and 3 weeks after stimulation respectively (135, 163). This study will investigate a new protocol involving 10 minutes stimulation, a 25 minute interval period and repeat 10 minutes stimulation.

6.2. Objectives

This study aimed to assess the effect of repeated a-tDCS on neuropathic pain levels in people with MS as a low-risk and non-invasive pain relief option. The hypotheses were that a five-day application of within-session repeated a-tDCS over M1 using a modified protocol would:
• Decrease pain levels significantly compared to sham tDCS.
• Decrease pain level significantly for up to 4 weeks.
• Improve the quality of life in MS patients significantly compared to sham tDCS.

6.3. Methods

Participants were identified and screened by a pain and rehabilitation physician. The inclusion criteria were:

• 18 years of age and over
• Diagnosis of MS based on McDonald’s criteria
• Level of pain on a visual analogue scale (VAS) of at least 40mm
• 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
• Patients were excluded if they:
  • Experiencing an acute exacerbation of MS
  • Had a skin condition on the scalp
  • Had existing metal in the head
  • Had existing implanted devices
  • Suffered from frequent or severe headaches
  • Were pregnant or breastfeeding

Patients were recruited from inpatients and outpatients of the Royal Melbourne Hospital, a tertiary hospital in Melbourne. Informed consent was obtained from all participants, and the study was approved by the Melbourne Health Human Research Ethics Committee (HREC/14/MH/115) prospectively registered. Once the participants had given consent, they were then randomised to active or sham intervention group via a computer-generated randomisation schedule as shown in Figure 18.
6.3.1. Transcranial Direct Stimulation

Participants had the intervention applied in a clinic room in a hospital environment to ensure their privacy. Application of tDCS was via a pair of surface electrodes and saline-soaked sponges measuring 5cm x 7cm. The anodal electrode was applied to the C3 or C4 EEG position contralateral to the side of pain; if both sides were affected, the side with higher pain level was selected. The cathode electrode was placed over the supraorbital area contralateral to the stimulated motor cortex (247). The stimulation was delivered via a Chattanooga Intellect Advanced Combo machine (DJO Global Inc. UK). A constant current of 2mA intensity was applied for 5 consecutive days at approximately the same time each day with the following protocol: 10 minutes stimulation, 25 minutes non-stimulation and then another 10 minutes stimulation.
6.3.2. Sham

Participants randomised to the sham group had the same setup as for the active group except that stimulation was turned on for 30 seconds but then ramped down to no stimulation; the generator fan was left ‘on’ but no active stimulation was undertaken.

6.3.3. Assessments

The primary outcome was measured by the Visual Analogue Scale (VAS) for pain level. This is a self-evaluation tool asking each participant to rate their pain level between 0mm indicating no pain to 100mm indicating worst pain possible (248). Secondary outcome measures included the Depression, Anxiety and Stress Scale (DASS), a 42 item self-report instrument to measure emotional states (249) and Short-Form McGill Pain Questionnaire (SFMPQ), which includes a 0-10 numerical scale and 15 descriptors for sensory and affect terms (250), the Neuropathic Pain Scale (NPS), a validated assessment tool to quantify and evaluate neuropathic pain (251) and the Multiple Sclerosis Quality of Life 54 (MSQOL54), a multidimensional disease-specific health-related quality of life measure (252). The VAS for pain and NPS were completed at the beginning and the end of each treatment session. The other outcome measures, the DASS, SFMPQ and MSQOL54, were completed at baseline and 4 weeks after the last intervention in addition to VAS and NPS. These timepoints were chosen to assess effects during the treatment phase and if there were ongoing effects after stimulation. Although masking was undertaken during treatment as stimulation was able to be ramped down without patients knowing, the assessor and operator was not masked.

6.3.4. Data Analysis

One-way repeated measures analysis of variance (ANOVA) was used to assess the effect of the a-tDCS intervention at the primary endpoint (session 5) on VAS and NPS and secondary outcome measures (DASS, SFMPQ and MSQOL54) at the end of week 4. One-way repeated measures ANOVA with GROUPS as a between-subjects factor was used to analyse the longitudinal data on VAS. A significance level of $P < 0.05$ was adopted for all comparisons. Post-hoc tests with Bonferroni correction for repeated analyses were performed where indicated. Means are reported unless
otherwise stated. Sample size estimation was calculated for a one-way ANOVA study. Sample sizes of 15 per group achieved 82% power to detect differences among the means versus the alternative of equal means using an F test with a 0.05 significance level. The size of the variation in the means was represented by their standard deviation which was 6.32. The common standard deviation within a group was assumed to be 15.00.

6.4. Results

A total of 30 participants were recruited in the study, with 15 participants randomised to each of sham and active groups. The baseline characteristics of both groups were similar; however, the number of female participants was higher than male participants. Participants had MS for more than 10 years and most had the relapsing-remitting type. The most common site for chronic neuropathic pain was bilaterally in the lower limbs in both groups. Most participants reported they were not on any analgesic medications. After the intervention, participants were asked if they thought they were in the treatment or sham group. A total of 56% of participants correctly reported whether they thought they had received sham or treatment.
Table 15: Characteristics of the participants for randomised controlled trial

After a 5-day course of a-tDCS, the VAS scores reduced significantly compared to sham tDCS (F(4,51)=5, P=0.00 (Figure 1). The VAS scores showed a significant reduction from day 4 (P=0.01) and remained significantly low up to week 2 post-treatment (P=0.01). For mean pain VAS, the within-subjects TIME factor was not significant. For between-subjects factors, there was a significant effect
for TIME (P=0.00) but not for the interaction between TIME and GROUP (P=.166). One-way ANOVA with TIME as the within-subjects factor was performed on secondary outcome measures. There were no statistically significant mean changes in MSQOL54, SFMPQ, NPS or DASS for sham or treatment group before treatment or 4 weeks follow-up (Table 2). The mean score difference between both scores was 1.22 which was statistically significant. The most common adverse effect was tingling during the stimulation and 1 individual experienced headache and phosphenes which did not persist after stimulation. Other adverse effects measured included scalp pain, sleepiness, trouble concentrating, mood changes which did not occur.

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T0</td>
<td>T1</td>
</tr>
<tr>
<td>VAS</td>
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<td>5.3(3)</td>
</tr>
<tr>
<td>NPS</td>
<td>51.9(16)</td>
<td>44.6(23)</td>
</tr>
<tr>
<td>MSQOL54 Physical</td>
<td>38.8(19)</td>
<td>39.6(18)</td>
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<tr>
<td>MSQOL54 Mental</td>
<td>53.2(21)</td>
<td>53.3(21)</td>
</tr>
<tr>
<td>DASS Depression</td>
<td>12.8(10)</td>
<td>12.5(12)</td>
</tr>
<tr>
<td>DASS Anxiety</td>
<td>12.1(8)</td>
<td>11.7(10)</td>
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<td>DASS Stress</td>
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<td>17.1(11)</td>
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<td>SFMPQ Sensory</td>
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<td>SFMPQ Affect</td>
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</tr>
</tbody>
</table>

Table 16: Summary of outcome measures [Mean (SD)] for randomised controlled trial

Legend:
*significant value p<0.05, Alpha value=0.05
Adjustment for multiple comparisons: Bonferroni, alpha value=0.05 T0=Baseline; T1=post-intervention (4 weeks)

VAS=Visual Analogue Scale; NPS= Neuropathic Pain Scale; MSQOL54= Multiple Sclerosis Quality of Life Score; DASS=Depression Anxiety Stress Score; SFMPQ= Short Form McGill Questionnaire; CI= Confidence Intervals

6.5. Discussion

This study showed that 5 consecutive days of a-tDCS could result in decreased pain intensity in chronic neuropathic pain in MS that lasts for up to 2 weeks compared with sham stimulation. This is consistent with other studies which have shown benefits in pain intensity reduction in other central nervous system disorders (135, 163, 253-255). However, this study did not support the initial hypothesis of a significant pain reduction lasting 4 weeks after treatment.
This study showed that a-tDCS is a safe intervention following this protocol, with no severe adverse effects. A common side-effect of mild tingling under the electrodes, only during stimulation, were reported by participants in the stimulation group, and sometimes by participants in the sham group (possibly through a placebo effect).

Unlike previous studies for a-tDCS for chronic pain in MS, this study used a unique protocol of 10 minutes stimulation followed by a 25 minutes interval period and another 10 minutes stimulation (135, 163). The interval period is postulated to prolong the effects of tDCS and modulation of corticospinal excitability through a cumulative effect on neuroplasticity. This cumulative effect is supported in the current literature which showed that a 25 minute interval period extended the period of increased corticospinal excitability to 2 hours in comparison to 45 minutes following a single 10-minute stimulation (83). This is also supported by other studies showing within-session repeated a-tDCS having enhanced corticospinal excitability in the M1 in comparison to a single stimulation session (256, 257).

However, the physiological mechanism of action is still mostly unknown. One postulated mechanism is that extending the duration of a single session would be limited by ‘neuronal counter-regulation’ which is a phenomenon preventing over-excitation of neurons (257). Hence repetitive and shorter tDCS sessions would help overcome this issue. Within-session tDCS has also been shown to have similar effects to long term potentiation which may play a role in enhanced excitability through neuroplasticity, NMDA and AMPA receptor modifications (257).

Neither group showed any significant improvement in secondary outcomes including DASS, MSQOL54 and SFM, which highlights that pain is a complex and multidimensional experience. Indeed, the literature supports this complex relationship between chronic pain and physical and mental domains (22). In addition to this, patients with MS commonly have multiple other physical and mental impairments which can affect their quality of life and experience of pain (258).

Limitations of this study include having a higher proportion of female participants with lower limb pain. However, our participants were representative of the prevalence of these characteristics in patients with MS (7). Currently, the literature has focused on a-tDCS for upper limb symptoms; it is believed to have poor penetration into deeper cortical levels to affect lower limb symptoms (259). However, there is increasing evidence that a-tDCS can also be efficacious for lower limb symptoms (260). Another limitation of this study is the lack of any objective measurement of the effects of tDCS on the excitability of M1, for example, the amplitude of motor-evoked potentials through transcranial magnetic stimulation (261). The dynamic nature of pain also limits this study. Pain and other symptoms of MS are dynamic and can fluctuate during the treatment and follow-up period and should be taken into account with the interpretation of the results (262). Pain VAS had been used as a primary outcome measure in this study. Although it is commonly used in clinical trials, there are inherent difficulties with this measurement tool, as it has been shown to be non-linear and standardised response means may vary and are highly subjective (263). As the assessor was not blinded to group allocation; and a high percentage of participants successfully reported their randomised group this study is still subject to bias. Single-blinding was chosen due to limited resources to set up double blinding.

As the assessment for blinding was after the treatment sessions, some of the participants may have already experienced a positive effect. The initial hypothesis relating to significant pain reduction up to
4 weeks was not supported; which could represent the need to repeat the treatment at 2 weeks but does support the use of an interval period during stimulation.

Strengths of the study include comparison with a control/sham group, and measuring not only pain intensity but the quality of life and depression, anxiety and stress scores. In comparison to previous studies of tDCS, this study has a larger sample size and more extended follow-up period. There were no drop-outs during the study, suggesting that this is a safe and feasible intervention.

Clinically, tDCS presents as a feasible treatment option in clinical practice. The application of tDCS may be suitable for patient use outside a hospital setting due to the ease of application. However, it would be important to set limits on the frequency and intensity due to the unknown long-term effects and safety profile beyond the tested protocols.

6.6. Summary of Chapter

Chronic neuropathic pain is a subcategory of chronic pain and is often difficult to treat with only pharmacological interventions. Pharmacological interventions include anticonvulsants and antidepressants and opioids but have limitations in the form of side effects such as drowsiness, nausea and vomiting, cognitive impairment and risks associated with dependence and tolerance.

There has been increasing literature on the neurobiology and processing of pain experience. M1, S1 and DLPFC have all been suggested to be involved in processing pain. The tDCS device is a non-invasive neurostimulation technique that utilises a constant low-intensity current (1-2mA). The primary mechanism of action of tDCS is based on the modification of the excitability of neuronal activity in parts of the cerebral cortex for pain processing and perception. The aim of this study was to assess the effect of repeated a-tDCS, and the hypotheses were that a five-day application of within-session repeated a-tDCS over M1 would decrease pain levels significantly compared to sham tDCS, decrease pain level significantly for up to 4 weeks and improve the quality of life in MS patients significantly compared to sham tDCS.

Participants were identified and screened by a pain and rehabilitation physician. The inclusion criteria were 18 years of age and over, diagnosis of MS, level of pain on a VAS of at least 40mm, Central pain, pain management stable for at least 2 months prior to treatment, no other nociceptive and peripheral neuropathic pain, psychiatric disease, headache or optic neuritis and able to understand English. Patients were recruited from inpatients and outpatients of the Royal Melbourne Hospital, a tertiary hospital in Melbourne. Informed consent was obtained from all participants, and the study was approved by the Melbourne Health Human Research Ethics Committee (HREC/14/MH/115).

Once the participants had given consent, they were then randomised to active or sham intervention group via a computer-generated randomisation schedule. Application of tDCS was via a pair of surface electrodes and saline-soaked sponges measuring 5cm x 7cm. The anodal electrode was applied to the C3 or C4 EEG position contralateral to the side of pain. VAS and secondary outcome measures measured the primary outcome included the DASS 42, SFMPQ, NPS and MSQOL54. The VAS for pain and NPS were completed at the beginning and the end of each treatment session. The other outcome measures, the DASS, SFMPQ and MSQOL54, were completed at baseline and 4 weeks after the last intervention.
A total of 30 participants were recruited in the study, with 15 participants randomised to each of sham and active groups. The baseline characteristics of both groups were similar; however, the number of female participants was higher than male participants. Participants had MS for more than 10 years and most had the relapsing-remitting type. The most common site for chronic neuropathic pain was bilaterally in the lower limbs in both groups. Most participants reported they were not on any analgesic medications. This study showed that 5 consecutive days of a-tDCS resulted in decreased pain intensity in chronic neuropathic pain in MS that lasts for up to 2 weeks compared with sham stimulation. This study showed that a-tDCS is a safe intervention following this protocol, with no severe adverse effects.

6.7. Conclusion

This study shows that repeated stimulation with a-tDCS for 5 days can reduce pain intensity for a prolonged period in patients with MS who have chronic neuropathic pain. This form of non-pharmacological treatment may provide a low-risk and non-invasive option for pain relief in this population. However, this study needs to be repeated with a larger sample size (including patients with MS with upper limb pain), a longer-term follow-up on analgesia and adverse effects, double-blinding and assessing blinding during treatment to reduce bias and explore repeating the treatment itself after 2 weeks, which may prolong the treatment effect. Along with the limitations of this study, a summary of all four studies, clinical applicability and limitations and strengths will be discussed in the final chapter.
Chapter 7. Conclusion and Discussions

7.1. Introduction

This Chapter discusses the findings of the four studies (Chapters 3 to 6) including:

- Methodological issues.
- Summary of each study.
- Comparison with other studies.
- Implications for clinical practice.

This thesis highlights the significance and impact of chronic pain in MS and the potential benefits of non-pharmacological management as part of a multidisciplinary and multimodal treatment regimen. Mixed methods were used for all four studies and achieved the objectives and provided support for the hypotheses as set out in Chapters 1 and 2). The work included a summary and evaluation of the current literature on chronic pain in MS and non-pharmacological treatment, observation of the effects of chronic pain and MS over time and the evidence for current non-pharmacological strategies such as interdisciplinary management and novel techniques such as neuromodulation.

7.2. Key Issues and Summary of Findings

7.2.1. Evidence for Non-pharmacological Management of Chronic Pain in Multiple Sclerosis

7.2.1.1. Key Issues

A systematic review of the current literature was performed using the GRADE approach, which is an internationally developed guideline and formal process to rate and evaluate systematic reviews. The following questions were explored in Study 1 (Chapter 3):

- Are non-pharmacological interventions (unidisciplinary and/or multidisciplinary rehabilitation) effective in reducing chronic pain in people with MS?
- 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 people with MS?

7.2.1.2. Summary of Findings

The study concluded that there was ‘very low level’ of evidence for non-pharmacological management of chronic pain in MS. The review included only RCTs, which involved non-pharmacological treatments such as TENS, tDCS, Tai Chi water exercises, tRNS, telephone self-management, hypnosis and reflexology. Although including only RCTs reduced the number of studies...
evaluated, the RCT is considered the best design to minimise bias. A review of the literature showed 558 studies which focused on non-pharmacological management for chronic pain in MS and ten studies were selected for final assessment.

7.2.2. Describing Longitudinal Data for Chronic Pain in Multiple Sclerosis

7.2.2.1. Key Issues
Longitudinal data has long been a significant gap in the literature and Study 2 explored longitudinal data in an Australian MS population up to 10 years. Key questions of the study included:

- What were the long-term effects (pain characteristics, healthcare utilisation, and disability) of chronic pain over ten years in MS in the community?
- Was there a carer required and carer strain?

7.2.2.2. Summary of Findings
This study showed that over time, there was a progression from single site pain locations to multiple pain locations, increased health utilisation, loss of independence, and deterioration in the quality of life and increase in the severity of chronic pain grading scale in comparison to the initial and 7-year cohort. By understanding the course of the condition and its impact on individuals with MS over ten years; it offers a greater understanding of prognostication especially in a chronic neurological disorder. This study shows that chronic pain is a significant ongoing issue for the majority of patients and there is an increased healthcare utilisation with fears and barriers to the use of medications noted to be an issue despite an increase in the use of pharmacological treatments. In addition, this study showed that 44% of MS patients now required a carer in the form of institutional care or family member. This prompts the need for effective treatment modalities.

7.2.3. Evidence for Interdisciplinary Management of Chronic Pain in Multiple Sclerosis

7.2.3.1. Key Issues
Current non-pharmacological practices for chronic pain have concentrated on interdisciplinary team management (99). The thesis included a retrospective audit on interdisciplinary management for chronic pain in MS and other central nervous system disorders. Questions answered in this study include:

- How effective is an outpatient interdisciplinary-based treatment for chronic pain in MS and central nervous system disorders?
- How to effectively evaluate a new clinical database?
7.2.3.2. Summary of Findings

This audit concluded that central nervous system disorders such as MS stroke, spinal cord injury, Parkinson's disease and traumatic brain injury could have similar improvements in pain self-efficacy and a decrease in pain catastrophisation compared to those without these comorbidities. This is an important study in investigation of current clinical practices and dispels the notion that those with a chronic neurological condition would perform poorly due to secondary impairments such as cognitive impairment, fatigue and physical weakness.

7.2.4. Evidence for Transcranial Direct Current Stimulation for Chronic Neuropathic Pain in Multiple Sclerosis

7.2.4.1. Key Issues

In addition to evaluating current treatment, this thesis outlines and explores novel non-pharmacological treatments for chronic pain in MS. A RCT compared a unique stimulation protocol of a 45-minute tDCS session with sham treatment. Questions explored in this study included:

- Does repeated a-tDCS decrease pain levels compared to sham tDCS?
- If so, are the effects maintained up to 4 weeks?
- Does repeated a-tDCS improve the quality of life in MS patients compared to sham tDCS?

7.2.4.2. Summary of Findings

This study showed an improvement in pain severity in the treatment group in comparison to placebo which lasted up to 2 weeks post-follow-up. There were no changes to the quality of life, depression or anxiety scores.

7.3. Discussions

Limited and very low level of evidence was concluded in a previous systematic review on non-pharmacological management of pain in MS (49). This systematic review did not find conclusive evidence to support any specific non-pharmacological intervention (49). The use of TENS showed a moderate effect size and was recommended as a potential treatment modality (49). Heterogeneous studies, risk of bias from small sample sizes and unclear in allocation or outcome concealment were common themes for the downgrading of evidence (49). In contrast, Study 1 focused on RCTs and highlights the increasing interest in neuromodulatory techniques in this updated review. Similar to the current literature, Study 1 found mixed outcomes, and mainly improvements in pain scores with less likelihood for changes in secondary outcomes such as quality of life and depression and anxiety scores (49). In summary there is a need for developing evidence for non-pharmacological management of chronic pain in MS.

Longitudinal studies for chronic pain in MS are limited to 5-7 years in duration and showed over-time participants reporting higher rates of pain, greater pain-related disability and reduced quality of life (8, 9). Study 2 is the first study to follow an Australian cohort with MS up to 10 years from initial
engagement. New findings show that over time there is a progression to greater bilateral pain sites, further deterioration in the quality of life and disability and the need for a carer. This study highlights the development of widespread pain and the impact of chronic pain on the individual and carer over-time.

The current evidence for the interdisciplinary management of chronic pain is limited. There is only one other study on this topic which concluded that those who participated in the program had a reduction in pain severity, improvement in function, depression and anxiety scores (99). Similarly, Study 3 also showed a reduction in pain catastrophisation and improvement in depression, anxiety and stress scores after interdisciplinary management (99). However, these findings were in an Australian and New Zealand cohort and made use of a new and large clinical database.

Study 4 is unique and explored a novel protocol for tDCS intervention for chronic neuropathic pain in MS which has an interval period between stimulation. Whereas the current most common protocol for tDCS stimulation involves 20 minutes of continuous stimulation daily for 5 days. (135). Study 4 also showed similar results to current evidence which is a reduction in pain severity scores which was maintained up to 1 to 3 weeks but did not show any changes to the quality of life scores (135, 163). This study supports the current evidence for tDCS use for chronic neuropathic pain in MS with a promising new protocol.

7.4. Strengths

Along with the limitations described there were strengths of this thesis which included:

- Having mixed-methods which added depth to the thesis. Different methodological studies included a systematic review, retrospective study, an observational and a prospective randomised controlled trial. A mixed-methods approach helped fill in gaps and limitations in the literature.

- This thesis focused on non-pharmacological management of chronic pain in MS. There has been a paucity of research in this area, and this thesis adds information on the use of new non-pharmacological techniques, evaluation of existing research databases and longitudinal data on chronic pain in MS.

- Although there are methodological concerns, there were, many strengths of each of the studies. Randomisation and blinding of the participants occurred, and there were no dropouts in each of the studies which are a reflection on the feasible design and safety aspects of the studies. The Cochrane review (Study 1) included only RCTs to ensure that the most up to date and standardised recommendations could be made on non-pharmacological treatments for chronic pain in MS.

- All studies were submitted to peer-reviewed journals for review by experts in the area to ensure high-quality evidence and presentation of the studies. Submission to journals was related to the thesis which involved either pain, MS or rehabilitation.
7.5. Limitations

Although this thesis adds to the existing literature, there were still limitations due to the clinical setting, methodological issues and feasibility of the studies. In addition to the individual limitations in each study, key methodological issues for the entire thesis are outlined below.

There were difficulties with study design which were potentially preventable. However, due to the complex nature of the interventions, access to resources and participants, this was difficult to avoid. Examples of limitations in study design included:

- A single site was used for the studies including participants that are known to the Royal Melbourne Hospital. This was difficult to avoid due to the feasibility of the staff involved in the research and limited funding. However, the inclusion of a retrospective study (Study 3) based on a database which involved 51 pain clinics in Australia and New Zealand was an opportunity to improve the heterogeneity of the study population. Recruitment of more sites would decrease bias, decrease generalisability and improve sample size.

- Participation by patients involved in Studies 2 and 4 was on a voluntary basis, and required participants to find time and travel distances for participation. This did add to the fatigue levels, the time taken out from their day, changes in arrangements and financial burden of patients. Participants were altruistic to participate and in the future financial support may help acknowledge the patients’ participation and ease the financial burden.

- The RCT (Study 4) was not double-blinded. Although blinding of the participants occurred, the assessors were not which increases the risk of bias and downgrade of the level of evidence. This was due to the due to the limited resources leading to limited set-up of concealment to the assessor and single-blinding was chosen.

- Due to the broad nature of the topic, not all non-pharmacological treatments were studied in this thesis. Non-pharmacological treatments range from physical exercises, psychotherapy, neuromodulation, ultrasound therapy and to study all these interventions would not be viable. It was decided to focus on neuromodulation and interdisciplinary management due to the gaps in the literature and form the basis for future studies.

- Research in non-pharmacological management is difficult due to operator-dependency of the interventions as in Study 4 which relied on the consistent administration of tDCS administration for each participant.

- A small sample size in Study 4 needs to be taken into account as a limitation. However, this was a pilot study and sample size was calculated to reach statistical significance.

7.6. Clinical Practice Implications

This thesis adds to the current literature and understanding of chronic pain in people with MS. The following recommendations can be made from the thesis from a clinical perspective:
• Chronic pain in MS is likely to be persistent, becomes more widespread and has a significant impact on health utilisation and pain-related disability.

• Clinicians should have an awareness of carer strain and disability associated with MS and chronic pain. This is important to prompt specialists in neurology and pain clinics to refer to other services for assessment and help.

• There should be greater collaboration between rehabilitation, pain specialists and neurologists for cross referrals, multidisciplinary meetings to improve access to specialised pain management strategies such as interdisciplinary management.

• Ideally there should be greater resources allocated to symptom-management services such as pain and rehabilitation to help fund improved clinical support.

• Clinicians should consider using screening tools for chronic pain which encapsulate a multidimensional aspect and easy to administer such as the Multidimensional Pain Inventory, McGill Pain Questionnaire and Brief Pain Inventory.

• Although there is a very low level of evidence for current non-pharmacological management for chronic pain in MS, this type of treatment modality should still be considered for clinical practice as part of multidisciplinary management and, low risk of side effects.

• Interdisciplinary management can be considered for those with chronic pain in central nervous system disorders to improve pain self-efficacy and decrease pain catastrophisation, as is the case for those without central nervous system disorders.

A repeated a-tDCS protocol with an interval period can reduce pain severity for neuropathic pain in MS for up to 2 weeks after treatment. There were no improvements in quality of life or depression and anxiety. This was a treatment option was not associated with serious adverse effects or dropouts

7.7. Research Implications

Although this thesis brings many insights into gaps the current literature, there are implications for future research. These include:

• If feasible, a double-blinded randomised controlled trial is recommended for prospective interventional non-pharmacological studies. This remains the gold standard of study design due to reduced bias (171).

• Other methodological considerations, as highlighted by systematic reviews, include allocation concealment, participant and personnel concealment, assessor concealment, random sequencing, selective reporting and reporting of results.

• Use of clinical databases enable investigation of important clinical questions in large groups of patients. The ePPOC database is improving over time in the accuracy of data entry and
patient participation. Given the wealth of information, outcome measures and data from multiple sites, other questions can be posed for other chronic pain in MS.

- With time, greater focus on specific non-pharmacological interventions should be considered for systematic reviews as current reviews are too broad.

- Focus on outcome measures other than pain severity is important, for example quality of life, depression and anxiety, self-efficacy and catastrophisation, due to the complex and multifaceted nature of pain. These should be considered in future research.

7.8. Conclusions

The studies reported in this thesis highlight the paucity of literature on non-pharmacological interventions for chronic pain in MS and the need for efficient and safe interventions. While they have contributed new findings in longitudinal data (Study 2), the effectiveness of interdisciplinary management (Study 3) and tDCS (Study 4), greater understanding of the mechanisms behind the interventions and research is required concurrently. More questions were raised in this thesis including pathophysiology of pain in MS, the prevalence of pain in MS and the efficacy of non-pharmacological interventions. In summary, the significance of non-pharmacological management of pain in MS has been highlighted and the methodology used should assist with future research and clinical implications.
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Appendices

Appendix 1. Published Papers

Non-pharmacological interventions for chronic pain in multiple sclerosis (Review)

Amatya B, Young J, Khan F

Amatya B, Young J, Khan F.
Non-pharmacological interventions for chronic pain in multiple sclerosis.
DOI: 10.1002/14651858.CD012522.pub2.

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Non-pharmacological interventions for chronic pain in multiple sclerosis

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ABSTRACT

Background
Chronic pain is common and significantly impacts on the lives of persons with multiple sclerosis (pwMS). Various types of non-pharmacological interventions are widely used, both in hospital and ambulatory/mobility settings to improve pain control in pwMS, but the effectiveness and safety of many non-pharmacological modalities is still unknown.

Objectives
This review aimed to investigate the effectiveness and safety of non-pharmacological therapies for the management of chronic pain in pwMS. Specific 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?

Search methods
A literature search was performed using the specialised register of the Cochrane MS and Rare Diseases of the Central Nervous System Review Group, using the Cochrane MS Group Trials Register which contains CENTRAL, MEDLINE, Embase, GINAHL, LILACS, Clinical trials.gov and the World Health Organization International Clinical Trials Registry Platform on 10 December 2017. Handsearching of relevant journals and scanning of reference lists of relevant studies was carried out.

Selection criteria
All published randomised controlled trials (RCTs) and cross-over studies that compared non-pharmacological therapies with a control intervention for managing chronic pain in pwMS were included. Clinical controlled trials (CCTs) were eligible for inclusion.

Data collection and analysis
All three review authors independently selected studies, extracted data and assessed the methodological quality of the studies using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) tool for best evidence synthesis. Pooling data for meta-analysis was not possible due to methodological, clinical and statistically heterogeneity of the included studies.

Non-pharmacological interventions for chronic pain in multiple sclerosis (Review)

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Main results
Overall, 10 RCTs with 565 participants which investigated different non-pharmacological interventions for the management of chronic pain in MS fulfilled the review inclusion criteria. The non-pharmacological interventions evaluated included: transcutaneous electrical nerve stimulation (TENS), psychotherapy (telephone self-management, hypnosis and electromyography (EMG) biofeedback), transcranial random noise stimulation (tRNS), transcranial direct stimulation (tDCS), hydrotherapy (AI Ckt) and reflexology.

There is very low-level evidence for the use of non-pharmacological interventions for chronic pain such as TENS, AI Ckt, tDCS, tRNS, telephone-delivered self-management program, EMG biofeedback and reflexology in pain intensity in pwMS. Although these were improved changes in pain scores and secondary outcomes (such as fatigue, psychological symptoms, sleep in some interventions), these were limited by methodological biases within the studies.

Authors’ conclusions
Despite the use of a wide range of non-pharmacological interventions for the treatment of chronic pain in pwMS, the evidence for these interventions is still limited or insufficient, or both. More studies with robust methodology and greater numbers of participants are needed to justify the effect of these interventions for the management of chronic pain in pwMS.

Plain Language Summary
[Non-pharmacological interventions for chronic pain in multiple sclerosis]
Review Question
Do non-medication treatments improve chronic pain in multiple sclerosis (MS) in comparison to inactive treatment?

Background
Chronic pain in people with MS (pwMS) is common, and treatment with medications can be associated with and limited by side effects such as confusion, falls, dizziness and constipation. Many non-medication treatments are used to treat chronic pain in pwMS, which include exercise, psychology, electrical stimulation therapy, reflexology and others.

Search Date
We included all randomised clinical trials (clinical studies where people are randomly put into one of two or more intervention groups), which were published up to December 2017.

Study Characteristics
Overall, we found 10 studies evaluating different non medication treatments to treat chronic pain in persons with MS. The treatments evaluated included: transcutaneous electrical nerve stimulation, transcranial direct stimulation, transcranial random noise stimulation, reflexology, psychotherapy and hydrotherapy. These studies included 565 participants and used a range of different methods to measure pain and other outcomes. Comparison groups also varied.

Key Results
Results from these studies show a very low level of evidence for the use of any non medication treatments for chronic pain in persons with MS.

Quality of Evidence
We assessed the overall quality of the studies as very low, as many studies included only small numbers of participants and had other methodological issues. More research with good methodological quality and greater number of participants are needed to determine the effectiveness of such treatments.
### SUMMARY OF FINDINGS FOR THE MAIN COMPARISON

Transcutaneous electrical nerve stimulation (TENS) compared to sham for chronic back pain in MS

**Patient or population:** Chronic back pain in MS

**Setting:** Participants from Multiple Sclerosis Society in Northern Ireland

**Intervention:** TENS

**Comparison:** Sham

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Impact</th>
<th>N of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reduction in pain intensity</strong></td>
<td>Decreased in low back pain scores over-time for all groups, however, none (1 RCT) reached clinical or statistical significance in VAS scores. No statistically significant changes in MPQ (Wasko 2005). VAS mean reduction for TENS low frequency at week 6 was -16.55 (weekly low back pain) and -10.76 (average low back pain).</td>
<td>90</td>
<td>★★★★☆  VERY LOW (^1) (^2)</td>
</tr>
<tr>
<td><strong>Reduction in disability</strong></td>
<td>No significant changes in disability measured by Roland-Morris Disability Questionnaire and SF-36 between treatment and placebo groups (Wasko 2005).</td>
<td>90</td>
<td>★★★★☆  VERY LOW (^1) (^2)</td>
</tr>
<tr>
<td><strong>Quality of Life</strong></td>
<td>No significant difference in quality of life measured by LMSQoL and SF-36 between treatment and placebo groups (Wasko 2005).</td>
<td>90</td>
<td>★★★★☆  VERY LOW (^1) (^2)</td>
</tr>
</tbody>
</table>

**Bi:** Barthel Index; **MPQ:** McGill Pain Questionnaire; **LMSQoL:** Leeds Multiple Sclerosis Quality of Life Questionnaire; **RMQ:** Roland Morris Disability Questionnaire; **SF-36:** Short Form 36; **VAS:** Visual Analogue Scale.
GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Downgraded two levels due to high risk of bias (unclear allocation concealment)

Downgraded two levels due to high risk of bias for imprecision (singular study of small sample size)
BACKGROUND

All technical terms used are listed in a Glossary (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 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 estimated 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) (Triulzi 2016; WHO 2008). It is more common in women (0.1 ratio) and patterns of MS presentation can vary significantly between individuals (Compton 1996; Derks 1978; Hammond 1988). The exact aetiology of MS is still unclear, but it is associated with an abnormal immune response within the CNS, possibly due to an infectious agent (Kurtzke 1983). Genetic risk has also been shown in recent literature, indicating an association between HLA-DRB1 and HLA-DR4 genes and MS susceptibility (O’Connell 2012). MS is associated with long-term physical, cognitive and behavioural disabilities, restrictions in participation, medical complications, and symptoms including pain (Khan 2007b; Khan 2013).

Description of the condition

According to the International Association of the Study of Pain (IASP), chronic pain is defined as “pain presenting continuously or intermittently for at least three months past the normal time of healing” (Vleeming 1994). Chronic pain impacts on activities of daily living, relationships, and social roles (Archibald 1994; Elde 2003; Khan 2007a; Svensson 2002; Warner 1991), interferes with work (Archibald 1994), and has been associated with increased psychological impairment, such as depression (Elde 2003). Many psychosocial facors 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 utilisation (Blyth 2003; Elde 2003; Mc 2014; Sullivan 1993; Vickery 1995). It is a significant health problem, impacting working-age populations and causing social disadvantage (Blyth 2003; Shihabuddin 2013), with an estimated cost of approximately $34 billion per annum in Australia alone (Blyth 2001).

In persons with MS (pwMS), symptoms such as headache and neuropathic extremity pain, back pain, painful spasms and Hermitte’s phenomenon are common and trigeminal neuropathic pain is least common. However, there is no confirmed prevalence and/or incidence rate of these symptoms in the literature. Pain can be a significant problem for a substantial proportion of pwMS (Elde 2003; Khan 2007a). It is estimated that 42% to 90% of pwMS experience pain (Clifford 1984; Iedema-Stone 2001; Mouton 1988; Smerger 1991; Verrone 1986), and occurs at all stages of the disease. MS-related pain can cause both acute and chronic symptoms. It is associated with active inflammation from the MS process itself (central neuropathic pain such as trigeminal neuropathic pain) and from MS-related complications (tonic spasms, headaches and musculoskeletal problems such as posture and gait anomalies) (Khan 2011). Pain is reported as one of the most severe symptoms in 8% to 32% of pwMS (Albert 1966; Schubas 1974; Smerger 1991) and is often co-occurring as a mix of acute, paroxysmal and chronic pain in the same or various parts of the body (Foley 2013; Von Korff 1992).

Based on the underlying pathophysiological mechanisms, MS-related pain can be classified into 5 categories (Triulzi 2013):

- **Neuropathic pain**, defined by the IASP (Merskey 1994) as pain arising directly from a lesion or disease affecting the somatosensory system (Treset 2008), which can consist of persistent extremity pain and dysesthesia, trigeminal neuropathic pain, and Hermitte’s phenomenon (defined as a transient sensation related to neck movement felt in the back of the neck, lower back and other parts of the body) (Al-Araj 2005).
- **Nociceptive pain**, either inflammatory or non-inflammatory, includes musculoskeletal and low back pain that may be posture-related, optic neuritis (Triulzi 2013), headaches and treatments-induced pain.
- **Psychogenic pain** is difficult to define and refers to somatiform 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 arthritic facial pain.
- **Mixed pain** encompasses a heterogeneous group of pain with different pathophysiological mechanisms caused by MS (such as 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 (Caster 2000; Rog 2005; Ross 2009; Shakespeare 2003) and non-pharmacological modalities, or a combination of both (Saliffuddin 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 (Ananya 2013; Boldi 2011). A wide range of non-pharmacological interventions have been trialled for the management of pain in pwMS. Previous studies (Iedema-Stone 2001; Khan 2007a; Khan 2013) have found that MS patients in the community setting frequently use...
a wide variety of non-pharmacological techniques, which include passive strategies such as transcutaneous electrical nerve stimulation (TENS), heat and/or cold therapy, supportive braces, alternative therapy; 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 adoption 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 distribution of central and peripheral pathways. CNS lesions causing hyperexcitability, and increased neuronal (nerve cell) activity at the site of the lesion in the spinal cord (Reisic 1998; Reivich 1999; Hass 2003; Lakhiani 2012). Chronic pain may 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 manner by each individual. It can arise both centrally and peripherally, and may be triggered by either a noxious or a non-noxious stimulus or can also occur spontaneously in the absence of any definable trigger (Reivich 1999; Jensen 1994; Jensen 1999). Due to this heterogeneity of chronic pain etiology among pwMS, modalities that act at different sites along the pain processing pathway may have variable degrees of effectiveness (Khan 2011; Lakhiani 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 with 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-behavioral therapy and other psychotherapies, on the other hand, utilise strategies that modify perception and cognition to enact a positive change in behaviour and mood.

Why it is important to do this review

Pain is prevalent in pwMS and tends to increase over time, due to the disease process itself and from MS-related complications, and is associated with a greater interference with pwMS' daily activities (Khan 2013). Several studies have demonstrated that those with higher pain grades reported more disability and healthcare visits, and lower quality of life (QoL) (Khan 2007a). Non-pharmacological therapies are widely used, both in hospital and ambulatory settings, to improve pain control, coping ability, daily function and QoL in pwMS. Chronic pain is found to be anecable to multidisciplinary rehabilitation management (Finlayson 2011; Karjalainen 2003; Khan 2007b; Kraft 2005; Safiuddin 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 trialled for chronic low back pain in pwMS and hypalgesic effects (Al-Subail 2003). Similarly, analgesic transcranial Direct Current Stimulation (tDCS) has demonstrated effectiveness in reducing central chronic pain in the MS population (Mori 2010). To our knowledge, there is only one published systematic review on non-pharmacological management in pwMS (Jawhar 2014), which excluded non-specific and non-therapeutic pain. This review identified the main categories of non-pharmacological interventions, which included education, electrical and physical therapy. The reviewers found that low frequency TENS had the greatest reduction in pain scores (Jawhar 2014). This systematic review did have several limitations, including inclusion of non-randomised clinical trials and pilot studies, and exclusion of various non-pharmacological interventions, such as acupuncture, massage therapy, and rehabilitation therapy such as transcutaneous stimulation (TMS) and tDCS. An updated systematic evaluation of the existing evidence is therefore needed to determine the effectiveness and safety of all non-pharmacological modalities to provide treating clinicians with clear guidance for clinical decision-making for appropriate pain management in pwMS.

OBJECTIVES

This review aimed to investigate the effectiveness and safety of non-pharmacological therapies for the management of chronic pain in persons with multiple sclerosis (pwMS).

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

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

METHODS

Criteria for considering studies for this review

Non-pharmacological interventions for chronic pain in multiple sclerosis (Review)

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Types of studies
All published randomised controlled trials (RCTs), including cross-over studies that compared non-pharmacological interventions with no treatment, sham and usual care, for managing chronic pain in pwMS were included. Clinical controlled trials (CC) were eligible for inclusion, but none were identified. We included only trials with a full journal publication, 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 excluded studies of experimental pain, observational studies, case reports, and clinical observations.

Types of participants
We included trials if the study population had a confirmed diagnosis of MS based on standard criteria (McDonald 2001) and participants were aged 18 years and older with chronic pain. All studies with participants with chronic pain or participants suffering from pain longer than three months were included, irrespective of the use of varying definitions for chronicity of pain. We included studies that recruited participants with the minimum levels of pain on visual analogue scale (VAS) of 3/10. Studies including participants with other diagnoses were excluded unless individual data for the pwMS could be obtained either from the published results or through contact with authors.

Types of interventions
All non-pharmacological interventions to manage chronic pain in pwMS delivered in any setting (inpatient, outpatient, community, or home-based) were included.

- 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, rTMS, dorsal root entry zone (DREZ) lesioning and others.

- Multidisciplinary rehabilitation programmes, defined as any co-ordinated 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 inducing chronic pain.

Control interventions that are likely used for comparison with the above mentioned interventions include no treatment, sham and usual care.

Types of outcome measures
Diverse outcomes were expected, given the varied presentations of pain-related problems and goals of treatment related to pain severity in MS.

Primary outcomes
The primary outcome determined 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, Zauder 2003), or specific pain scales such as the McGill Pain Questionnaire (MPQ, Melzack 1975), Short Form McGill Pain Questionnaire (SF-MPQ, Melzack 1997), or Brief Pain Inventory (BPI, Cleeland 1989), and others (subjective or objective). We used the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) (Devereaux 2008) criteria, defined as:

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

Secondary outcomes
Due to the multidimensional model of pain, we included secondary outcomes determining whether the change in pain by the intervention affects the other specific outcome(s) measured by validated tools, which included:

- other symptoms or impairments, such as spasticity, fatigue, e.g. Multiple Sclerosis Spasticity Scale (MSSS, 88, Hobart 2006);
- Modified Ashworth Scale (MAS, Ansari 2009); Fatigue Impacts Scale (FIS, Fisk 1994); Modified Fatigue Impact Scale (MFHI, Larson 2013); Fatigue Severity Score (FSS, Kuyk 1989);
- functional activity, e.g. Functional Independence Measure (FIM, Granger 1999); Barthel index (BI, Mahoney 1965);
- Rawlins Morrison Disability Questionnaire (RMQ, Severs 2016);
- psychosocial outcomes, e.g. Beck Depression Inventory (BDI, Beck 1961); Depression, Stress and Anxiety Scale (DASS, Lovibond 1995); Hospital Anxiety Depression Scale (HADS, Snith 2003); Patient Health Questionnaire 9 (PHQ-9, Kroenke 2001);
- restriction in participation/impact on carers, e.g. Caregiver Strain Index (CS, Robinson 1983);
- vocational outcomes, e.g. Work Instability Scale (WIS, Gilworth 2003);
- quality of life, e.g. Multiple Sclerosis Quality of Life (MSQOL-54, Vickery 1995); Short Form Health Survey (SF-36, Ware 2000); Leeds Multiple Sclerosis Quality of Life (LMSQOL, Enari 2016); Multiple Sclerosis Impact Scale (MSIS-29, Hobart 2001).
• withdrawals, due to lack of efficacy;
• outcomes that reflect utilisation of healthcare 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, that may jeopardise the person or may require intervention.

Timing of outcome measures
We divided outcome time points into short term (up to three months) and long term (greater than three months) from the start of the intervention.

Search methods for identification of studies
We considered articles in all languages with a view to translation, if necessary.

Electronic searches
The Information Specialist searched (up to 10 December 2017) the Trials Register of the Cochrane MS and Rare Diseases of the CNS Group, which, among other sources, contains trials from:
• Cochrane Central Register of Controlled Trials (CENTRAL) (2017, issue 12);
• MEDLINE (via PubMed) (1950 to 10 December 2017);
• Embase (via Embase.com) (1980 to 10 December 2017);
• Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCOhost) (1981 to 10 December 2017);
• Latin American and Caribbean Health Science Information Database (LILACS) (Bireme) (1982 to 10 December 2017);
• ClinicalTrials.gov (http://clinicaltrials.gov/); and
• World Health Organization (WHO) International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/).

The keywords that were used 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 MS and Rare Diseases of the CNS Group’s module.

In addition we searched the following databases:
• PsycINFO (1980 to 10 December 2017), (Appendix 3);
• Allied and Complementary Medicine Database (AMED) (1985 to 10 December 2017) (Appendix 4); and
• MANTIS/Ovid (for most recent data available) (Appendix 5).

Searching other resources
We conducted an expanded search to identify articles potentially missed through the database searches and articles from grey literature. These were:
• relevant articles from Medline (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, JV) independently screened and shortlisted all abstracts and titles of studies identified by the search strategy for appropriateness based on the selection criteria. The same two review authors (BA, JV) independently reviewed the abstract of each study from the short list of potentially appropriate studies for inclusion or exclusion. The full text of the article was obtained to determine if the study met the inclusion/exclusion criteria. Articles assessed in full text that did not meet the inclusion criteria were listed in the Characteristics of excluded studies with the reasons for exclusion. If no consensus was met about the possible inclusion/exclusion of any individual study, a final consensus decision was made by discussion with the third author (FK). Review authors were not masked to the names of the author(s), institution(s) or publication source at any level of the review. Further information was sought about the method of randomisation and other methodological issues, if required. We excluded 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).

Data extraction and management
Two review authors (BA, JV) independently extracted the data from the included trials using a standardised form and entered the data into the RevMan software (Review Manager 2014), which included:
• 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;
Assessment of risk of bias in included studies

Two review authors (FL, YJ) independently assessed 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 assessed the following for each study:

- **Random sequence generation (selection bias)**: we assessed the method used to generate the allocation sequence as low risk of bias (any truly random process, random number table, computer random generation) and unclear risk of bias (when the method is not clearly stated). We excluded studies with a non-random process.
- **Allocation concealment (selection bias)**: we assessed the method used to conceal the allocation to interventions prior to assignment that determined whether the intervention allocation could have been foreseen in advance, during recruitment, or changed after assignment. We assessed methods as low risk of bias (telephoned or central randomisation; consecutively numbered, sealed, opaque envelopes) and unclear risk of bias (when method is not clearly stated).
- **Blinding of participants and personnel (performance bias)**: we assessed the methods used to blind study participants, personnel.
- We assessed methods as low risk of bias (study states it was blinded and describes the method used to achieve the blinding) and unclear risk of bias (study stated it was blinded but did not provide adequate description of how this was achieved).
- **Blinding of outcome assessment (detection bias)**: we assessed the methods used to blind the allocated interventions by outcome assessors. We assessed methods as low risk of bias (study states blinding of outcome assessments ensured) and unclear risk of bias (when method is not clearly stated) and high risk (no blinding of outcome assessment).
- **Incomplete outcome data (attrition bias)**: we assessed 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 'last observation carried forward' analysis or both), unclear risk of bias (used 'last observation carried forward' analysis or high risk of bias (used 'complete' analysis).
- **Selective reporting (reporting bias)**: we assessed the methods used to report outcomes and selective reporting. We assessed methods as low risk of bias (all of the study's prespecified outcomes and protocol is available), unclear risk (insufficient information) or high risk (not all of the study's prespecified outcomes is reported).

Other bias: we assessed other bias as low risk (free of other sources of bias), unclear risk (insufficient information) or high risk (potential source of bias).

Any disagreements or lack of consensus was resolved by the third review author (FL).

Measures of treatment effect

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

Unit of analysis issues

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

Dealing with missing data

Insufficient data that were not available were reported but not included in the final analysis. We assumed the data were missing at random and only available data were analysed.

Assessment of heterogeneity

We conducted statistical analysis, as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011).

Assessment of reporting biases

Publications bias was minimised by performing comprehensive searches of multiple databases (Egger 1998). Where data were not reported in full for certain outcomes, we contacted the trial authors for the full dataset or the reason for not publishing the data. Where sufficient studies (at least 10) were identified, we assessed potential biases of reporting using funnel plots and visual inspection for
symmetry according to the approach outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011).

**Data synthesis**

A meta-analysis was not possible due to methodological, clinical and statistically heterogeneity of included studies. We therefore pooled results from clinically similar studies for the meta-analysis, if sufficient studies were available.

**Subgroup analysis and investigation of heterogeneity**

Treatment effects in subgroups of trials were analysed and compared. With data that were available, we performed subgroup analysis for the following:

- sex (male/female);
- type of MS (relapsing remitting, progressive);
- Expanded Disability Status Scale (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 were unable to perform sensitivity analysis because the findings from included studies evidence were too small to allow reliable analysis. Further, we were not able to pool results from chronic pain of different central origins in the primary analyses, due to lack of data.

'Summary of findings' table

We presented the main results of the review in 'Summary of findings' (SoF) tables, according to recommendations described in Chapter 11 of the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0). We included an overall grading of the evidence for the following patient-important outcomes:

- reduction in pain intensity;
- reduction in disability;
- improvement in quality of life;
- reduction in fatigue;
- reduction in depression and anxiety;
- reduction in pain interference, depression, fatigue;
- improvement in pain, self efficacy, patient activation, health-related quality of life, social role satisfaction, resilience, positive and negative affect.

We graded the quality of evidence for each outcome considering study limitations, indirectness, inconsistency, imprecision of effect estimates, and risk of reporting bias. According to the software GRADEpro 2016, we assigned four levels of quality of evidence: high, moderate, low, and very low.

**RESULTS**

**Description of studies**

See Characteristics of included studies and Characteristics of excluded studies

**Results of the search**

Electronic and manual searches identified 538 references (MEDLINE = 361; Embase = 138; CINAHL = 21; Central = 5; CRD database = 6; Handsearch = 7; WHO portal = 6; Clinicaltrials.gov = 14). Of these, 30 passed the first screening, review and were selected for closer review. In total, 10 articles fulfilled the inclusion criteria and were included. See Figure 1 for Study flow chart.
Figure 1. Study flow diagram.

658 of records identified through database searching

22 of additional records identified through other sources

563 of records after 18 duplicates removed

562 of records screened

532 of records excluded

20 of full-text articles excluded, with reasons:
Chronic pain not a criteria: 13
No pain outcome measures: 2
Not controlled clinical trial: 3
Abstract: 2

30 of full-text articles assessed for eligibility

10 of studies included in qualitative synthesis
Included studies

Overall, 10 randomised controlled trials (RCTs) (Ayache 2016; Castro-Sanchez 2012; Elide 2015; Hughes 2009; Jensen 2009; Jensen 2016; Moi 2010; Nasari 2016; Palma 2016; Warke 2006) involving 957 participants fulfilled the inclusion criteria for this review. Two studies were conducted in Northern Ireland (Hughes 2009; Warke 2006); three studies in the USA (Elide 2015; Jensen 2009; Jensen 2016); two studies were from France (Ayache 2016; Palm 2016); and one study each from Spain (Castro-Sanchez 2012), Italy (Moi 2019) and Iran (Nasari 2016). The included studies evaluated various non-pharmacological interventions, which included:

- one study (Warke 2006) evaluated the effects of TENS, which used alternating currents by cutaneous electrodes positioned near the painful area;
- two studies (Ayache 2016; Moi 2010) investigated the effects of tDCS, which used a low current directly delivered to the brain for neuromodulation;
- two studies (Hughes 2009; Nasari 2016) investigated the effects of self-esteem, which involved the managing of the feet that correspond to different parts of the body;
- one study (Castro-Sanchez 2012) evaluated hydrotherapy;
- three studies (Elide 2015; Jensen 2009; Jensen 2016) evaluated psychotherapy, which used a telephone-based self-management educational program, self-hypnosis and neurofeedback;
- one study (Palm 2016) evaluated rTMS, which used a form of neuromodulation through rapidly changing current frequencies.

Excluded studies

Detailed descriptions of excluded studies with reasons for exclusion is provided in Characteristics of excluded studies. Overall, 20 studies were excluded (Anninos 2016; Buxton 2016; Barlow 2009; Cattaneo 2014; Doulatzad 2012; Hasapour-Delkordi 2015; Hasapour-Delkordi 2016; Jensen 2007; Jensen 2011; Martinelli 2015; Matlabi 2005; McGuire 2015; Neghaban 2013; Oken 2006; Pizzuti 2013; Pozzilli 2002; Sessa 2013; Sessa 2011; Sessa 2006; Van der Linden 2013). Reasons for exclusion included: 13 studies did not define chronic pain as a criteria (Doulatzad 2012; Hasapour-Delkordi 2015; Hasapour-Delkordi 2016; Martinelli 2015; Matlabi 2005; McGuire 2015; Neghaban 2013; Oken 2006; Pizzuti 2013; Pozzilli 2002; Sessa 2011; Sessa 2006; Van der Linden 2013), two were abstracts only (Cattaneo 2014; Jensen 2007), three were not clinical controlled trials (Backus 2016; Jensen 2011; Sessa 2013), and two trials did not have pain as an outcome (Anninos 2016; Barlow 2009).

Risk of bias in included studies

For a summary, please see Risk of bias’ tables in the Characteristics of included studies and Figure 2 and Figure 3.
Figure 2. ‘Risk of bias’ summary: review authors' judgements about each risk of bias item for each included study.
Figure 3. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Allocation

**Random sequence generation**
Nine studies were considered to have a low risk of bias for this domain (Ayache 2016; Castro-Sanchez 2012; Elde 2015; Hughes 2009; Jensen 2009; Jensen 2016; Mori 2010; Nazari 2016; Wurke 2006). Palm 2016 was considered to have an unclear risk of bias for this domain as randomization was not discussed.

**Allocation concealment**
One study (Elde 2015) was considered to have a low risk of bias for allocation concealment as the allocation sequence was concealed from the research assistants who enrolled participants via a limited access database program. The other nine studies were considered to have an unclear risk of bias for allocation concealment (Ayache 2016; Castro-Sanchez 2012; Hughes 2009; Jensen 2009; Jensen 2016; Mori 2010; Nazari 2016; Palm 2016; Wurke 2006).

Blinding

**Blinding of participants and personnel (performance bias)**
Blinding of participants for performance bias was assessed as high risk in two studies (Castro-Sanchez 2013; Jensen 2003), as the study could not guarantee the study was blinded and no blinding was reported, respectively. Two studies had an unclear risk of bias (Jensen 2016; Nazari 2016). The remaining six studies had a low risk of bias (Ayache 2016; Elde 2015; Hughes 2009; Mori 2010; Palm 2016; Wurke 2006).

**Blinding of outcome assessment (detection bias)**
Two studies were assessed as unclear risk for blinding of outcome assessment as blinding was not described (Nazari 2016; Palm 2016) and two studies were assessed as high risk (Elde 2015; Jensen 2016).

**Incomplete outcome data**
All studies provided information on participant withdrawal and loss to follow-up. Two studies (Elde 2015; Hughes 2009) reported loss of participants to follow-up and were assessed as high risk; the remaining studies were considered to be at low risk of bias.

**Selective reporting**
All included studies assessed pre-specified primary and secondary outcomes and were assessed as 'low' risk.

Other potential sources of bias
Two studies (Palm 2016; Wurke 2006) were assessed as unclear risk as funding was received but it was unclear if it had an impact on results.
Effects of interventions

See: Summary of findings for the main comparison

Transcutaneous Electrical Nerve Stimulation (TENS) compared to Sham for Chronic Back Pain in Multiple Sclerosis (MS); Summary of findings 2: At Cui Exercises compared to Sham for Chronic Musculoskeletal pain in Multiple Sclerosis (MS); Summary of findings 3: Transcranial Direct Current Stimulation (tDCS) compared to Sham for Chronic Neuropathic Pain in Multiple Sclerosis (MS); Summary of findings 4: Transcranial Random Noise Stimulation (tRNS) compared to Sham for Chronic Neuropathic Pain in Multiple Sclerosis (MS); Summary of findings 5: Telephone-Delivered Education Group compared to Sham for Chronic pain in Multiple Sclerosis (MS); Summary of findings 6: Hypnosis compared to relaxation control for chronic pain in Multiple Sclerosis (MS); Summary of findings 7: Neurofeedback compared to relaxation control for chronic pain in Multiple Sclerosis (MS); Summary of findings 8: Botulinum toxin injection compared to Sham for Chronic Pain in Multiple Sclerosis (MS)

As aforementioned, the included studies used a wide range of non-pharmacological interventions and used various assessments relating to pain measures. Key findings based on the interventions evaluated and summary of findings are described below and tabulated in 'Summary of Finding' tables. A meta-analysis was not possible and narrative descriptions of the findings are presented instead.

Transcutaneous electrical nerve stimulation (TENS)

One study (Warke 2006) evaluated the effects of TENS on chronic low back pain in persons with multiple sclerosis (pwMS). (Summary of findings for the main comparison)

In this study, 90 participants were randomised into three groups (N = 30 in each): low-frequency TENS, high-frequency TENS and placebo (sham). There was a decrease in low back pain scores overtime in all three groups in visual analogue scores (VAS), however, none reached statistical significance. Similarly, no statistically significant changes in the McGill Pain Questionnaire (MPQ) was found in all three groups. All three groups showed improvement in patient-reported disability scores (Roland Morris Disability Questionnaire (RMDQ)), however, it was not statistically significant.

Hydrotherapy

One RCT (N = 73 participants) (Castro-Sánchez 2012) evaluated the effectiveness of At Cui water-based exercise program compared to placebo. The participants in the intervention group received At Cui water exercises twice a week for 20 weeks. The authors reported significant reduction in pain VAS score in the treatment group immediately after treatment (P = 0.028), which was maintained up to 30 weeks (P = 0.047). There were no statistical significance changes in the control group at any time point. Similarly, compared to the control group, the treatment group showed a significant pain reduction at week 20 in MPQ and was maintained up to week 24 (P < 0.021). There were significant decreases in disability (RMDQ) scores in both groups at week 20. The treatment group also showed a significant decrease in spasm VAS score at week 20 compared to the control group (P = 0.039). Both groups showed a significant reduction in the Multiple Sclerosis Impact Scale 29 (MSIS-29) psychological score at week 20. (Summary of findings 2)

Transcranial direct stimulation (tDCS)

Two studies (Ayache 2016; Mori 2019) evaluated the effectiveness of tDCS in pwMS. (Summary of findings 3)

One RCT (Ayache 2016) (N = 16) randomised participants to either anodal tDCS (N = 8) or sham (N = 8) groups. The findings showed a statistically significant difference between before and after treatment for mean pain VAS score in the treatment group (P = 0.024). There were no statistically significant changes in the sham group. Active stimulation resulted in significant improvement in pain (Brief Pain Inventory (BPI) global score) (P = 0.02), but no significant effects on severity, or in the sham group. There were no significant differences observed through simulation for both groups for functional and psychological outcomes for MSIS and HADS.

In another study (Mori 2019), participants (N = 19) were randomised to anodal tDCS (N = 10) or sham (N = 9) groups. There were statistically and clinical significant changes for pain VAS and MPQ scores in the anodal tDCS group compared to the control sham group (P = 0.03). The authors also reported statistically significant changes for the treatment effect over time in quality of life (QoL) for the Multiple Sclerosis Quality of Life-54 (MSQOL-54) and the Short Form McGill Pain Questionnaire (SF-MPQ). There were no statistically significant changes for other psychological outcomes (Beck Depression Inventory (BDI) and VAS for anxiety) in both groups.

Transcranial random noise stimulation (tRNS)

One RCT (N = 16 participants) (Talm 2016) examined the effect of tRNS in comparison with the sham. The authors found no statistically significant changes for mean pain VAS score before and after treatment for both tRNS and sham groups. There was a significant change in BPI in the treatment group but not in the sham group. Further, there were no statistically significant changes for any psychological and functional outcomes (Hospitcal Anxiety and Depression Scale (HADS); Modified Fatigue Impact Scale (MFIS) scores in both groups. (Summary of findings 4)

Psychotherapy

Three RCTs (Eldes 2015; Jensen 2009; Jensen 2016) evaluated different forms of psychotherapy. (Summary of findings 5, Summary of findings 6 and Summary of findings 7)
One RCT (Lipska 2015) (N = 163 participants) compared a telephone-delivered self-management program with the control group receiving telephone-delivered educational program. The authors reported that a 50% reduction in one or more symptoms (fatigue, pain interference and depression severity) was achieved in 59% of the intervention group and 46% of the control group. However, this was not statistically significant. There were no clinical significant changes in pain intensity after treatment and at follow-up in both intervention and control group. The authors reported statistically significant improvements in all secondary outcomes (fatigue, self-efficacy, pain interference quality of life) for both groups, which was maintained up to six and 12-month follow-up.

Another RCT (Jensen 2009) evaluating the effectiveness of self-hypnosis or pain in preMSC, randomised (N = 22) participants to self-hypnosis (N = 15) and progressive muscle relaxation (N = 7) groups. The authors found statistically and clinically significant changes post- and post-treatment in the hypnosis group in reduction in daily pain intensity but not in the control group (P < 0.001). There was also statistically significant change post- to post-treatment in the hypnosis group but not in the progressive relaxation group for pain interference (P = 0.001).

Another RCT (Jensen 2016) randomised (N = 29) participants to the EEG biofeedback (N = 10) group or relaxation control group (N = 19). Both groups improved in pain scores four weeks after treatment and at one-month follow-up; however this was not statistically significant. There was a moderate to large improvement in the neurofeedback group after treatment (effect size, ES = 0.78) and 1 month after follow-up (ES = 1.04), but effect size of improvement was not different in the control group. There were improvements for other pain scores (BPI, worst pain intensity) and fatigue severity in the intervention group with moderate to large effect sizes.

**Reflexology**

Reflexology was evaluated in two studies (Hughes 2009; Nazari 2016). **Summary of findings**

One RCT (Hughes 2009) (N = 71 participants) compared reflexology with a control group with sham intervention. The authors found clinical and statistically significant reduction in pain VAS scores at 10 weeks compared to baseline in both groups (P = 0.0001), which was maintained up to 22 weeks. Both groups demonstrated significant reduction in MPQ pain rating index at week 10. For MPQ pain index there were no changes in the sham group, but a statistically significant change at week 10 for the reflexology group (P < 0.01). Both groups showed a significant reduction in disability score measured by RMDQ at 10 weeks. Further, both groups had a similar statistically significant decrease in VAS pain score by the end of the treatment period. Both groups showed significant reductions in physical and psychological subscales of MSIS at week 10. There was a significant reduction by week 10 in both groups in fatigue (MFS, Fatigue Severity Scale (FSS) scores), with no significant differences between groups. There was a significant reduction in psychological outcomes (BDI scores) by week 10 in both groups. Functional improvements (measured by the Barthel Index (BDI)) in both groups remained stable throughout treatment by week 10.

Another RCT (Nazari 2016) (N = 75 participants) randomised participants to either reflexology, relaxation or control groups. There were statistically and clinical significant differences in pain scores in the reflexology group (P < 0.001) and relaxation group (P = 0.01) pre- and post-treatment, while no significant changes were found in the control group (P = 0.34).
**ADDITIONAL SUMMARY OF FINDINGS**

**Patient or population:** chronic musculoskeletal pain in people with MS  
**Setting:** participants were recruited from MS Association of America in Spain  
**Intervention:** A: Chi exercises  
**Comparison:** sham  

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<th>Outcomes</th>
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<th>n of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
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<tr>
<td>Reduction in pain intensity</td>
<td>Significant reduction in pain scores measured by VAS in the treatment group immediately after treatment and no significant change from baseline in the control group. Pain VAS at week 20 was 55% (experimental) and 22% (control). Significant pain reduction for MPQ in the treatment group and no significant change from baseline in the control group (Castro-Sanchez 2013).</td>
<td>70 (1 RCT)</td>
<td>VERY LOW 1.2</td>
</tr>
<tr>
<td>Reduction in disability</td>
<td>Significant reduction in disability measured by RMQD in intervention and control group at week 20 (Castro-Sanchez 2013).</td>
<td>73 (1 RCT)</td>
<td>VERY LOW 1.2</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>Both groups showed a significant reduction in the psychological subscale of the MSQOL at week 20. Treatment group showed significant score reduction but the control group showed no significant difference with baseline score in the physical subscale at week 20 (Castro-Sanchez 2013).</td>
<td>73 (1 RCT)</td>
<td>VERY LOW 1.2</td>
</tr>
</tbody>
</table>
Reduction in Fatigue assessed with MFIS

| Treatment group showed a significant 73  |
| score reduction compared with baseline (9 RCT) at week 20, but no significant difference in control group. Treatment group showed a significant reduction in cognitive fatigue compared with the control group (Castor-Brenchley, 2013). |

**MFIS**: Modified Fatigue Impact Scale, **MPQ**: McGill Pain Questionnaire, **MSIS-29**: Multiple Sclerosis Impact Scale-29, **RMDQ**: Roland Morris Disability Questionnaire, **SF-36**: Short Form-36, **VAS**: Visual Analogue Scale

**GRADE Working Group grades of evidence**

- **High certainty**: We are very confident that the true effect is close to that of the estimate of the effect.
- **Moderate certainty**: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low certainty**: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- **Very low certainty**: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect.

1 Downgraded two levels because the single study was considered at serious risk of performance bias (blinding of participants and personnel) and unclear risk of allocation concealment.
2 Downgraded two levels due to imprecision (small sample size).
**Transcranial direct current stimulation (tDCS) compared to sham for chronic neuropathic pain in MS**

**Patient or population:** chronic neuropathic pain in MS  
**Setting:** community neurology clinic  
**Intervention:** tDCS  
**Comparator:** sham

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Impact</th>
<th>-- of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reduction in Pain Intensity</strong></td>
<td><strong>assessed with VAS, UP-MPQ</strong></td>
<td>36</td>
<td><img src="image" alt="Image" /> VERY LOW 1.1</td>
</tr>
<tr>
<td>Mean pain VAS showed significant decrease after active tDCS (mean baseline 51.2; after treatment 43.1) but no significant change for sham (mean baseline 52.1; after treatment 50.3). BPI global score for active tDCS (2) showed significant improvement on the interference sub-scale but no significant effects on the severity sub-scale (Vajecky 2016). Significant main effect of time for decreased daily pain VAS (Mori 2010).</td>
<td><img src="image" alt="Image" /></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Reduction in Fatigue</strong></td>
<td><strong>assessed with MIFIS</strong></td>
<td>36</td>
<td><img src="image" alt="Image" /> VERY LOW 1.3</td>
</tr>
<tr>
<td>There was no significant difference in 16 fatigue measured by the MIFIS between (1 RCT) groups (Vajecky 2016).</td>
<td><img src="image" alt="Image" /></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Reduction in Depression and Anxiety</strong></td>
<td><strong>assessed with BDI, HADS, VAS for anxiety</strong></td>
<td>36</td>
<td><img src="image" alt="Image" /> VERY LOW 1.3</td>
</tr>
</tbody>
</table>
| No significant differences in depression and anxiety were observed for both groups on HADS (Vajecky 2016).  
No significant changes for BDI and VAS for anxiety with time as within subject and group of treatment as between subjects. (Mori 2010) | ![Image](image)                |                                    |
**Improvement in QoL** assessed with MOL154

| Significant effect of time and group x time interaction for improved quality of life measured by the MOL154 (Mook 2018). |

**GRADE Working Group grades of evidence**

**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect.

**Moderate certainty:** We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

**Low certainty:** Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

**Very low certainty:** We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

*Downgraded one level for risk of bias (the two studies at unclear risk of bias in allocation concealment)*

*Downgraded two levels for high risk for imprecision (small sample sizes of both studies)*
### Transcranial Random Noise Stimulation (TRNS) compared to sham for chronic neuropathic pain in MS

**Patient or population:** chronic neuropathic pain in MS  
**Setting:** hospital MS clinics  
**Intervention:** TRNS  
**Comparator:** sham

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Impact</th>
<th>-- of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in pain</td>
<td>No statistically significant change for 16 mean pain VAS before and after 50.1; mean VAS after 47.2 and sham groups (mean VAS before: 52.1; mean VAS after: 50.3) No statistical significance before and after elimination sham and treatment for BPS (Palm 2016).</td>
<td>16 (1 RCT)</td>
<td><strong>VERY LOW</strong> 1.2</td>
</tr>
<tr>
<td>Reduction in anxiety and depression</td>
<td>No statistical significance before and after for treatment and sham for mean HADS (Palm 2016).</td>
<td>16 (1 RCT)</td>
<td><strong>VERY LOW</strong> 1.2</td>
</tr>
<tr>
<td>Reduction in fatigue</td>
<td>No statistical significance before and after for treatment and sham for mean total score (Palm 2016).</td>
<td>16 (1 RCT)</td>
<td><strong>VERY LOW</strong> 1.2</td>
</tr>
</tbody>
</table>

BPS: Beck Pain Inventory; HADS: Hospital Anxiety and Depression Scale; MFIS: Modified Fatigue Impact Scale; VAS: Visual Analogue Scale

GRADE Working Group grades of evidence  
**High certainty:** We are very confident that the true effect is close to that of the estimate of the effect  
**Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.  
**Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect  
**Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect.
1 Downgraded two levels because the single study was considered at high risk of bias (unclear risk of bias in randomisation sequence generation, allocation concealment and blinding of outcome assessors)

2 Downgraded two levels due to high risk for imprecision (single study of small sample size)
## Telephone-delivered education compared to sham for chronic pain in MS

**Patient or population:** Chronic pain in MS  
**Setting:** Participants’ homes across United States  
**Intervention:** Telephone-delivered education group  
**Comparator:** Sham

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Impact</th>
<th>N of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in pain interference, depression, fatigue assessed with BPI, PHQ-9, SF-36</td>
<td>59% of telephone self-management group and 46% of telephone education group had &gt; 50% reduction in 1 or more symptoms (fatigue, pain, depression), but not statistically significant (Blinde 2013);</td>
<td>163 (1 RCT)</td>
<td>VERY LOW††††</td>
</tr>
<tr>
<td>Improvement in pain, self-efficacy, patient activation, health-related quality of life, social role satisfaction, resilience, positive and negative affect assessed with AIMS, BPI, SF-36, SF-12, UWMS, Patient Activation Measure, Medical Outcomes Study 2 Item Short Form Health Survey, Patient Reported Outcomes Measurement Information System Short Form, Connor-Davidson Resilience Scale</td>
<td>Statistically significant improvements in all secondary outcomes for fatigue, pain interference, self-efficacy and QoL compared with telephone education group (Blinde 2013);</td>
<td>163 (4 RCT)</td>
<td>VERY LOW †††</td>
</tr>
</tbody>
</table>

**BPI:** Brief Pain Inventory; **SF-36:** Modified Fatigue Impact Scale; **MPQ:** McGill Pain Questionnaire; **PHQ-9:** Patient Health Questionnaire 9; **QoL:** quality of life; **UWMS:** University of Washington Quality of Life Scale

**GRADE Working Group grades of evidence**

- **High certainty:** We are very confident that the true effect is close to that of the estimate of the effect.
- **Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- **Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect.
1 Downgraded two levels due to high risk of bias (the singular study at high risk of bias in blinding of outcome assessor and participant).
2 Downgraded two levels due to high risk of bias for imprecision (small sample size).
<table>
<thead>
<tr>
<th>Study Title</th>
<th>Reduction in pain intensity</th>
<th>Reduction in pain intensity</th>
<th>Reduction in pain intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>Very high</td>
<td>Very low</td>
<td>Very low</td>
</tr>
<tr>
<td>Study 2</td>
<td>Very high</td>
<td>Very low</td>
<td>Very low</td>
</tr>
</tbody>
</table>

**Outcome 1:**
- Statistically significant change in post-winter estimates.
- Improvement in the intervention group (ICF) was significant.
- Not significant in the control group.

**Conclusion:**
- The intervention was significantly more effective than the control group.
Neurofeedback compared to relaxation/control for chronic pain in MS

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Impact</th>
<th>~ of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in pain intensity assessed with Numerical Rating Scale (averages)</td>
<td>Both groups improved soon after intervention and at 1-month follow-up, but not statistically significant. Average mean pain intensity for intervention (before 5.30; after: 4.41; 1 month 3.38) and control (before 5.24; after 4.32; 1 month 4.31). Worst pain intensity score improvements in intervention (before 8.69; after 5.90; 1 month 5.18) and control (before 6.36; after 5.49; 1 month 5.55) (Jensen 2016).</td>
<td>20 (1 RCT)</td>
<td>☀ ☀ ☀ ☀ VERY LOW 1.2</td>
</tr>
<tr>
<td>Reduction in fatigue assessed with FSS</td>
<td>Improvements over time pre to post-treatment in intervention (Jensen 2016).</td>
<td>20 (1 RCT)</td>
<td>☀ ☀ ☀ ☀ VERY LOW 1.2</td>
</tr>
<tr>
<td>Reduction in pain interference assessed with BPI</td>
<td>BPI score improvement in both groups (Jensen 2016).</td>
<td>20 (1 RCT)</td>
<td>☀ ☀ ☀ ☀ VERY LOW 1.2</td>
</tr>
</tbody>
</table>

BPI: Brief Pain Inventory; FSS: Fatigue Severity Scale

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect is close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect.

* Downgraded two levels due to high risk for bias (unclear allocation concealment and no blinding of outcome assessors)
2 Downgraded two levels due to high risk for imprecision (singular study of small sample size)
| Reduction in Fatigue assessed with MFS, FSS | MFS physical sub scale score significantly improved in both sham and treatment by week 10. Significant reduction in MFS cognitive sub scale score in both sham and treatment by week 10. Significant reduction in MFS psychological sub scale in both sham and treatment by the end of the treatment period. Both sham and treatment demonstrated a significant reduction in fatigue by week 10 (Hughes 2009). | QCCQ | VERY LOW 1.2 |
| Reduction in depression assessed with BDI-II | Both sham and treatment groups showed a significant reduction in values by week 10 (Hughes 2009). | QCCQ | VERY LOW 1.2 |
| Reduction in Spasms assessed with VAS for spasm | Both sham and treatment demonstrated a statistically significant decrease in spasm by the end of the treatment (Hughes 2009). | QCCQ | VERY LOW 1.2 |

BDI: Beck Depression Inventory; BDI: Barthel Index; FSS: Fatigue Severity Scale; MFS: Modified Fatigue Impact Scale; MSIS-29: Multiple Sclerosis Impact Scale-29; VAS: Visual Analogue Scale

GRADE Working Group grades of evidence
- High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
- Moderate certainty: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low certainty: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
- Very low certainty: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect.

1 Downgraded two levels due to high risk of attrition bias and unclear risk of bias in blinding and allocation concealment
2 Downgraded two levels due to high risk of imputation (small sample size)
**DISCUSSION**

**Summary of main results**

Overall, 10 RCTs with 565 participants fulfilled the inclusion criteria of this review, which evaluated various non-pharmacological interventions for the management of chronic pain in persons with multiple sclerosis (pwMS), which included: physical therapy (Ai Chi water exercise), psychotherapy (telephone self-management, cognitive restructuring, neurofeedback and hypnosis), near-infrared transcranial direct current stimulation (tDCS), transcranial random noise stimulation (tRNS), reflexology and transcutaneous electrical nerve stimulation (TENS). The included trials were heterogeneous in terms of type and intensity of interventions evaluated and outcome measures used. The study quality varied and the pooled evidence was limited due to high risk of bias, underpowered studies (small sample size) and lack of data on changes of pain outcomes in majority of the studies. Therefore, quantitative synthesis was not possible and a qualitative synthesis of 'best evidence' was summarised.

The findings suggest that there is very low level evidence for the following interventions:

- **TENS in reducing lower back pain.**
- **Ai Chi water exercises in improving pain intensity which was maintained up to 30 weeks.** There were also improvements in spasm, quality of life (QoL) and fatigue.
- **tDCS in reduction in pain intensity and up to three weeks after treatment and improvement in QoL.** But not in fatigue and anxiety and depression.
- **tRNS in improving pain scores, depression or anxiety or fatigue.**
- **Telephone-delivered self-management program for the reduction of pain intensity, catastrophisation, self-efficacy, fatigue and QoL in chronic pain.**
- **EEG biofeedback for reduction in pain intensity and fatigue and pain interference.**
- **Reflexology in reducing pain intensity, disability, fatigue, psychological and physical impact and depression up to 22 weeks.**

**Overall completeness and applicability of evidence**

Despite a comprehensive search of the literature, only 10 trials evaluating a wide variety of non-pharmacological treatments fulfilled the inclusion criteria. Due to the quality of the published studies, many aspects of non-pharmacological interventions for multiple sclerosis (MS) pain remain unknown. Further, there were only few studies (which were heterogeneous) that evaluated a given type of intervention, which did not permit pooling data for quantitative analyses. There are other non-pharmacological interventions (e.g., yoga, massage therapy and radial shock wave therapy) which have been used for pain relief in pwMS, however, studies evaluating these interventions did not fulfil the inclusion criteria for this review. Cost-effectiveness of the intervention and reporting of safety or adverse events for participants were not evaluated in any of the included trials. Overall, the review identified many issues relating to the studies evaluating non-pharmacological interventions in chronic pain in MS which could affect the overall completeness and applicability of evidence. The gaps in the evidence base for non-pharmacological management of chronic pain in pwMS include the following:

- **Limited and/or lack of high-quality evidence for the effectiveness of non-pharmacological interventions.**
- **Complexity and different mechanisms related to chronic pain in MS.**
- **Broad range of non-pharmacological interventions used in different context and with scope.**
- **Difficulty of blinding and incorporation of a control or placebo.**
- **Lack of use of Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMPCACT) recommendations for measures of significance and standardised measurement outcomes.**
- **Difficulty with knowing the effective dose or duration for many non-pharmacological interventions due to lack of definitive mechanisms.**

Non-pharmacological interventions are therapist- and operator-dependent and may be prone to multiple combined mechanisms or 'bundled effects' (Bernert 2011). Suggestions for future improvements in quality of evidence include robust studies emphasising on the mechanisms of pain in MS.

**Quality of the evidence**

All 10 included studies were rated as 'very low' quality for methodological evidence due to risk of bias and flaws in their methodological design (Figure 2; Figure 9).

- **Lack of reporting in IMPCACT suggestion of > 30% or 50% change in pain scores for clinical significance.**
- **Limited reporting of complete data.**
- **Lack of allocation concealment (Avache 2016; Castro-Sanchez 2012; Hughes 2009; Jensen 2009; Jensen 2016; Nazari 2016; Palm 2016; Warke 2006).**
- **Unclear in the reporting, of study authors' conflicts of interest, funding sources (Palm 2016; Warke 2006).**

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Non-pharmacological interventions for chronic pain in multiple sclerosis (Review)

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• Difficulty controlling for therapist-dependent bias, patient motivation and activity/interactions outside of treatment.

In summary, these limitations affected the quality of the evidence and highlights the importance of good methodological practices in research. This is specially important given the difficulty in recruitment of targeted study cohorts (with adequate sample sizes) and difficulties associated with controlling for patients’ personal and other confounding factors such as, patient motivation and self-efficacy, comorbidity and activity level outside of therapy programmes), which influence compliance and delivery of therapy, thus impacting on outcomes.

POTENTIAL BIAS IN THE REVIEW PROCESS

The review authors followed a number of steps to ensure the reduction of bias in the review process. First, the review authors independently reviewed and assessed all articles. Second, the review authors adhered strictly to the inclusion and exclusion criteria for the studies and extraction and interpretation of the data, and followed the GRADE handbook. However, a number of limitations in the methodological quality of the review itself, and the completeness of the retrieved literature, cannot be ruled out. Despite the extended range of terms that were used to capture the widest possible selection of the relevant literature, we were not able to rule out some degree of selection bias from the literature search (van Walder 2003). Possibility of publication bias cannot be omitted as we were not able to include negative trials or other trials which are yet to be published in academic literature (Egger 1998). Further, reference bias (Goesche 1997) is a further possibility, as we searched only reference lists within the relevant papers for additional articles. We welcome contact from any reader who are aware of important high-quality studies which are not included in this review.

AGREEMENTS AND DISAGREEMENTS WITH OTHER STUDIES OR REVIEWS

There are limited systematic reviews in the area of non-pharmacological management of chronic pain in MS. This review highlights existing evidence and gaps in the literature. There are some similarities which are consistent between this review and another published non-Cochrane systematic review (Jawahar 2014). However, there are methodological differences of this review and the review by Jawahar et al (Jawahar 2014), specifically inclusion of only high quality studies (randomised controlled trials (RCTs) and clinical controlled trials (CCTs)) and use of standardised tools (The Cochrane Handbook for Systematic Reviews of Interventions 2011) and the GRADE for the methodology and interpretation of findings. We think this review addressed the methodological issues in systematically reviewing, the evidence for the management of chronic pain in pwMS (Bennett 2011). This is reflected in the findings of various issues within the included studies in this review, included blinding, small sample sizes, determination of the right dose/duration of treatment and focus on other outcome measures other than pain intensity such as adverse effects and patient compliance and adherence to therapy.

AUTHORS’ CONCLUSIONS

Implications for practice

Despite use of a range of non-pharmacological interventions for the treatment of chronic pain in persons with multiple sclerosis (pwMS), this review found ‘very low-level’ evidence for the use of such interventions. Therefore, it is difficult to recommend routine use of non-pharmacological interventions alone for the treatment of chronic pain in an MS population. However, findings suggest that use of non-pharmacological intervention in combination with pharmacological agents is reasonable. The findings of this review also highlight the existing gaps in the literature and emphasise the need for robust evidence to support these modalities. Ongoing involvement is vital to build evidence from everyday clinical practice. The clinical applicability of findings of this review need to be confirmed in future studies with robust study design, larger sample sizes and long-term follow-up.

Implications for research

This review shows that there are significant gaps in the literature on non-pharmacological management of chronic pain in MS. Future research implications include the following:

• Robust studies with reduced risk of bias, with adequate allocation, randomisation procedures

• Standard reporting of pain as defined by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) (Dworkin 2008)

• Reporting pain measures desired by patients (Moore 2013)

• Appropriate and careful selection of study cohort and larger sample size

• Emphasis on details of pain mechanism, localisation pattern, severity and impact on everyday function

• Impact and burden on carer and family, or both

• Intervention-related adverse effects/complications

• Long-term impact of interventions

• Cost associated with the interventions
ACKNOWLEDGEMENTS

We are grateful to the Cochrane Multiple Sclerosis and Rare Diseases of the CNS Group Editorial Board for their support and assistance and Dr Kevin Young for his assistance in protocol preparation. We also like to thank Professor Andrew Moore and the editors for reviewing the manuscript.

REFERENCES

References to studies included in this review

Ayache 2016 (published data only)

Castro-Sanchez 2012 (published data only)

Ehde 2015 (published data only)

Hughes 2009 (published data only)

Jensen 2009 (published data only)

Jensen 2016 (published data only)

Merli 2010 (published data only)

Nazari 2016 (published data only)

Palm 2016 (published data only)

Waks 2006 (published data only)

References to studies excluded from this review

Aussine 2016 (published data only)

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Doulatshah SN, Nowreza K, Doulatshah AN, Nezhadvandegan LM. The effects of pranayama, tanha and...

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Bulld I, Eriksson LG, Brinchmann MW, Rie PA, Von Essen P. Non-pharmacological interventions for chronic pain in people with spinal cord injury. *Cochrane Database of Systematic Reviews* 2011;11. DOI: 10.1002/14651858.CD009177.pub2

Cleeland 1988

Clifford 1984

Compton 1998

Cutter 2000

Dodd 1978

Drewes 2008

Egger 1998

Elde 2003

Elde 2005

Ensari 2016

Fifalayoa 2013

Fisk 1994

Foley 2013

Forsythe 1973

Gibborth 2003

Goetzschke 1987
Granger 1990

Hammond 1988

Hanso 2003

Harling 1998

Heckman-Stone 2001

Higgins 2011

Hobart 2001

Hobart 2006

Hunt 2004

Jawahar 2011

Jensen 1994

Jensen 1999

Jensen 2001

Karjalainen 2003

Khan 2007a

Khan 2007b

Khan 2011

Khan 2013

Kraft 2005

Kroenke 2011

Krupp 1989

Krauze 1983

Lahdes 2012
Larson 2013

Lovibond 1995

Ma 2014

Mahoney 1965

McDonald 2001

McGill 1975

McGill 1987

Merskey 1994

Moore 2013

Moulia 1988

MS Society 2011

O’Gorman 2012

Review Manager 2014 (Computer program)

Robinson 1983

Rog 2005

Rossi 2009

Saifuddin 2014

Shahbazian 2013

Sheapsey 2003

Shibasaki 1974

Simmons 1960

Smith 2003

Storeger 1991

Stevens 2016

Sullivan 1993

Svendsen 2003
Thomas 2006

Treado 2008

Triandos 2010

Trneci 2013

van Tonder 2003

Vermote 1986

Vickers 1995

Von Korff 1992

Wace 2006

Waller 2004

Wardill 1991

WHO 2008

Zaider 2003

References to other published versions of this review

Amaya 2017

* Indicates the major publication for the study

Non-pharmacological interventions for chronic pain in multiple sclerosis (Review)
## Characteristics of Studies

**Characteristics of included studies** [ordered by study ID]

### Ayache 2016

| Methods | • Randomised sham-controlled trial, crossover, and double-blinded study  
• Randomisation through computer generation  
• Study conducted in France  
• Allocation concealment not stated |
|---|---|
| Participants | **Population source**: participants enrolled from Neurology Department of Henri Mondor Hospital  
**Numbers**: randomised 16, anodal transcranial direct current stimulation 8, sham 8  
**Inclusion criteria**: age 18-70 years, definitively diagnosed with multiple sclerosis according to McDonald’s criteria, right-hand dominance based on Edinburgh Inventory, neuropathic pain >3 months as per Neuropathic Pain Symptom Inventory, VAS >40 over average 1 week  
**Exclusion criteria**: multiple sclerosis relapses within last 2 months, changes in pharmacological and physiotherapy in last month, presence of comorbid neurodegenerative or psychiatric disorders, history of substance abuse, absence of measurable pain-related evoked potentials at right hand, severe deficits in visual acuity and fields by examination, severe upper limb impairment by Medical Research Council for muscle power  
**Age**: mean age 48.9 years, range 38-67 years  
**Gender**: women 13, men 3  
**Type of MS**: relapsing remitting 11, secondary progressive 4, primary progressive 1  
**Pain type**: Neuropathic pain |
| Interventions | **Treatments**: anodal tDCS, 2mA current  
**Control**: sham tDCS  
**Duration**: 3 consecutive days of tDCS stimulation (20-minute sessions), at least 3 weeks washout period |
| Outcomes | • VAS  
• BPI  
• NHP  
• FADS  
• CRO  
• CGI |
| Notes | **Funding**: authors had received grants and gave lectures.  
**Conflicts of interest**: authors declared no commercial or financial relationships that could act as conflict of interest |

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
</table>

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### Ayache 2016 (Continued)

<table>
<thead>
<tr>
<th>Bias Type</th>
<th>Risk Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>The randomisation schedule was generated prior to the beginning of the study using a dedicated software.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No information provided.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>Participants were blind to treatment.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>Participants were blind to treatment.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Attrition rate reported. None lost to follow-up.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All outcomes reported.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No other bias detected.</td>
</tr>
</tbody>
</table>

### Castro-Sanchez 2012

<table>
<thead>
<tr>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Randomised controlled trial</td>
</tr>
<tr>
<td>• Study conducted in Spain</td>
</tr>
<tr>
<td>• Randomisation through computer generation</td>
</tr>
<tr>
<td>• Allocation concealment not described</td>
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</table>

<table>
<thead>
<tr>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population source</strong>: participants were recruited from MS Association of Almeria in Spain</td>
</tr>
<tr>
<td><strong>Number</strong>: randomised 73, At Chi 86, control 37</td>
</tr>
<tr>
<td><strong>Inclusion criteria</strong>: MS diagnosis, age between 18 and 75 years, VAS pain score &gt; 4 for at least two months, EDSS ≤ 7.5</td>
</tr>
<tr>
<td><strong>Exclusion criteria</strong>: treatment with another complementary and alternative medicine (either current or within the previous 3 months, relapse requiring hospitalisation or steroid treatment within the past 2 months)</td>
</tr>
<tr>
<td>Age: experimental group (mean age 46 years, range 25-75), control group (mean age 50 years, range 29-75)</td>
</tr>
<tr>
<td><strong>Gender</strong>: experimental group (25 women, 10 men), control group (24 women, 13 men)</td>
</tr>
<tr>
<td><strong>Type of MS</strong>: experimental group 46 primary progressive, 9 secondary progressive, 21 unknown, control group 9 primary progressive, 12 secondary progressive, 16 unknown</td>
</tr>
<tr>
<td><strong>Pain type</strong>: musculoskeletal pain (back, cervical, legs, feet, arms, shoulder)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment</strong>: At Chi exercises</td>
</tr>
<tr>
<td><strong>Control</strong>: relaxation</td>
</tr>
<tr>
<td><strong>Duration</strong>: 20 weeks (twice a week), 4 sessions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
</tr>
<tr>
<td>• VAS</td>
</tr>
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### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Computer-generated randomised list</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Allocation concealment not described</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>High risk</td>
<td>Study could not guarantee that participants were blinded to the nature of their group because they were all members of the same association</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>Researcher blinded to group allocation</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>None lost to follow-up</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All outcomes reported</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No other bias detected</td>
</tr>
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</table>

### Elde 2015

**Methods**
- Randomised controlled trial, single-blinded, parallel group and single centre
- Study conducted in the USA
- Randomisation through computer generation
- Allocation by blinded access database program

**Participants**
- **Population source:** recruited from University of Washington Department of Rehabilitation Medicine Research. Registry and advertisements through National MS organisations. Flyers and referrals from University of Washington Multiple Sclerosis Centre
- **Numbers:** randomised 163, telephone self-management 78, control (telephone education) 88
- **Inclusion criteria:** ≥18 years, self-reported physician diagnosis of MS and 1 or more...
of the following: (1) moderate depressive symptoms indicated by a score of 10 to 14 on the PHQ-9, presence of chronic pain (average pain intensity 5 in the past week) or significant fatigue symptoms, defined as a score >10 on the 5-item (MFIS)

**Exclusion criteria:** cognitive impairment (1 error on 6-item Cognitive Screen), psychotherapy more than once a month, had participated in another study for fatigue, depression, or pain, moderate-severe to severe depressive symptoms (PHQ-9 score 15)

**Age:** treatment group (mean age 51 years, range 25-76), control group (mean age 53.2 years, range 26-76)

**Gender:** treatment group (women 67, men 8), control group (women 75, men 13)

**Type of MS:** treatment group (relapsing-remitting 46, progressive 29), control group (relapsing-remitting 45, progressive 43)

**Pain type:** chronic pain

### Interventions

**Treatment:** telephone self-management skills training  
**Controls:** education on MS symptoms  
**Duration:** 8 weekly individual telephone calls delivered, 45-60 minute sessions

### Outcomes

**Primary**  
- MFIS  
- BPI  
- PHQ-9  

**Secondary**  
- Pain NRS  
- SES  
- PANAS  
- PAM  
- SF-36 Health Survey  
- Patient Reported Outcomes Measurement Information System  
- Connor Davidson Resilience Scale

### Notes

**Funding:** not described  
**Conflicts of interest:** not described

### Risk of bias

<table>
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<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Random numbers were generated by computer software</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>The allocation sequence was concealed from the research assistants who enrolled participants via a limited access database program</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>On 2 occasions research assistants became aware of a participant's allocation</td>
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---

**Non-pharmacological Interventions for chronic pain in multiple sclerosis (Review)**  
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<table>
<thead>
<tr>
<th></th>
<th>High risk</th>
<th>On 2 occasions research assistants became aware of a participant's allocation</th>
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<td>Blinding of outcome assessment (detection bias)</td>
<td>All outcomes</td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>All outcomes</td>
<td>High risk  For the telephone self-management group there were 16 withdrawals during sessions and 4 during assessments. For the control group there were 6 withdrawals during sessions and 2 withdrawals during assessments</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All outcomes reported</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No other bias detected</td>
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**Hughes 2009**

<table>
<thead>
<tr>
<th>Methods</th>
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<tbody>
<tr>
<td></td>
<td>• Randomised controlled trial, double-blinded</td>
</tr>
<tr>
<td></td>
<td>• Study in Northern Ireland</td>
</tr>
<tr>
<td></td>
<td>• Randomisation through computer-generated lists</td>
</tr>
<tr>
<td></td>
<td>• Allocation concealment not described</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
<th>Population source: responses to advertisement in local advertisement and MS charities Numbers: randomised 71, intervention 35, sham 36</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Inclusion criteria: 18-75 years of age, definite diagnosis of MS, pain greater than 4 on VAS of at least 2 months, EDSS of 7.5</td>
</tr>
<tr>
<td></td>
<td>Exclusion criteria: previous experience of reflexology, participation in research studies currently or within the previous 3 months relapse (requiring hospitalisation or steroid treatment) within the past 2 months</td>
</tr>
<tr>
<td></td>
<td>Age: reflexology group (mean age 50 years, range 26-75), sham group (mean age 53, range 34-74)</td>
</tr>
<tr>
<td></td>
<td>Gender: reflexology group (36 women, 5 men), sham group (29 women, 7 men)</td>
</tr>
<tr>
<td></td>
<td>Type of MS: relapsing remitting multiple sclerosis (3), secondary progressive (6), primary progressive (1), relapsing remitting (2), primary progressive (1), secondary progressive (1), unknown (9)</td>
</tr>
<tr>
<td></td>
<td>Pain type: musculoskeletal (low back pain, leg/foot/shoulders/hips/arms/eye)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Intervention: reflexology by accredited reflexology specialist. Controls: standardised foot massage</th>
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<tbody>
<tr>
<td></td>
<td>Duration: 45-minute sessions weekly for 10 weeks</td>
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<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Primary</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>VAS (Pain)</td>
</tr>
<tr>
<td></td>
<td>Secondary</td>
</tr>
<tr>
<td></td>
<td>VAS (weekly pain scores)</td>
</tr>
<tr>
<td></td>
<td>MPQ</td>
</tr>
<tr>
<td></td>
<td>PRI</td>
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<td>FPI</td>
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### Risk of bias

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<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Randomised by computer-generated list</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Allocation concealment not described</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>Participants were blinded to group allocation</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>Investigator who was blinded to group allocation</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>Five participants were lost to follow-up</td>
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<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All outcomes in the review reported</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No other bias detected</td>
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</tbody>
</table>

### Methods

- Randomised controlled clinical trial
- Study conducted in the USA
- Randomisation through computer-generated lists
- Allocation concealment not described

### Participants

**Population source:** recruited from previously completed survey of study of pain  
**Numbers:** randomized 22, self-hypnosis first 8, self-hypnosis 7, progressive muscle relaxation 7  
**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  
Age: mean age 51.7 years (27-75 years)  
Gender: 16 women, 6 men  
Type of MS: not reported  
Pain type: not reported |
|---|
| **Intervention** | **Control:** self-hypnosis training  
**Duration:** 10 sessions |
| **Outcomes** | **Primary outcome:**  
NRS  
**Secondary outcomes:**  
EPI  
**Amount and effects of hypnosis (pain relief 0 to 10, number of days listened, usual number of times listened, hours of relief they experience after listening)** |
| **Notes** | **Funding:** not reported  
**Conflicts of Interest:** not reported |

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Participants were randomly assigned via a computer-generated list of random numbers</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No allocation concealment described</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>High risk</td>
<td>No blinding reported</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>Blinding of assessors</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Two of the participants did not provide complete data</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All data presented</td>
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<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No other bias detected</td>
</tr>
<tr>
<td>Methods</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------------------------------</td>
<td>------------------------------------------------------------------</td>
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<tr>
<td>• Randomised controlled trial</td>
<td></td>
<td></td>
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<tr>
<td>• Study conducted in the USA</td>
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<tr>
<td>• Randomisation through computer-generated lists</td>
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<td></td>
</tr>
<tr>
<td>• Allocation concealment not described</td>
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<table>
<thead>
<tr>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population source:</strong> 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</td>
</tr>
<tr>
<td><strong>Numbers:</strong> 20, EEG biofeedback (NF-HYP) 10, relaxation control group 10</td>
</tr>
<tr>
<td><strong>Inclusion criteria:</strong> 18 years or older, &gt;= 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</td>
</tr>
<tr>
<td><strong>Exclusion criteria:</strong> 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</td>
</tr>
<tr>
<td><strong>Age:</strong> mean age (50 years)</td>
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<tr>
<td><strong>Gender:</strong> 12 women, 7 men</td>
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<tr>
<td><strong>Type of MS:</strong> relapsing remitting 12, secondary progressive 5, primary progressive 0, progressive relapsing 0, unknown 2</td>
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<tr>
<td><strong>Pain type:</strong> not reported</td>
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<tr>
<td><strong>Adverse effects:</strong> not reported</td>
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<table>
<thead>
<tr>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention:</strong> hypnosis preceded by neurofeedback</td>
</tr>
<tr>
<td><strong>Controls:</strong> hypnosis preceded relaxation</td>
</tr>
<tr>
<td><strong>Duration:</strong> 5 sessions of self-hypnosis training (1 face-to-face and 4 pre-recorded sessions)</td>
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<tr>
<td><strong>Neurofeedback:</strong> 20 minutes of neurofeedback</td>
</tr>
<tr>
<td><strong>Relaxation:</strong> 20 minutes of relaxation through headphones</td>
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<table>
<thead>
<tr>
<th>Outcomes</th>
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</thead>
<tbody>
<tr>
<td><strong>Primary outcomes:</strong></td>
</tr>
<tr>
<td>• Average NRS</td>
</tr>
<tr>
<td><strong>Secondary outcomes:</strong></td>
</tr>
<tr>
<td>• NRS (Worst pain intensity)</td>
</tr>
<tr>
<td>• FSS</td>
</tr>
<tr>
<td>• BPI</td>
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<table>
<thead>
<tr>
<th>Notes</th>
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<tbody>
<tr>
<td><strong>Funding:</strong> not reported</td>
</tr>
<tr>
<td><strong>Conflicts of interest:</strong> not reported</td>
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<table>
<thead>
<tr>
<th>Risk of bias</th>
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</thead>
<tbody>
<tr>
<td><strong>Bias</strong></td>
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<tr>
<td><strong>Authors’ judgement</strong></td>
</tr>
<tr>
<td><strong>Support for judgement</strong></td>
</tr>
<tr>
<td><strong>Random sequence generation (selection bias)</strong></td>
</tr>
<tr>
<td>Low risk</td>
</tr>
<tr>
<td>Randomisation through computer-generated numbers</td>
</tr>
<tr>
<td><strong>Allocation concealment (selection bias)</strong></td>
</tr>
<tr>
<td>Unclear risk</td>
</tr>
<tr>
<td>No allocation concealment described</td>
</tr>
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### Jesen 2016 (Continued)

<table>
<thead>
<tr>
<th>Blinding of participants and personnel (performance bias)</th>
<th>Unclear risk</th>
<th>Blinding was not described</th>
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<tbody>
<tr>
<td>All outcomes</td>
<td></td>
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</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>High risk</td>
<td>No blinding for assessors</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>One participant’s data not collected</td>
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<tr>
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<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All outcomes reported</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No other bias detected</td>
</tr>
</tbody>
</table>

### Mari 2010

| Methods | • Randomised controlled trial and double-blinded  
          | • Study conducted in Italy  
          | • Randomisation through computer-generated lists  
          | • Allocation concealment not described |
|---------|--------------------------------------------------|
| Participants | **Population source:** randomised 19 intervention group (transcranial direct current stimulation) 10, control 9  
                **Inclusion criteria:** diagnosis of MS established by McDonald's criteria, chronic neuropathic pain >1 month (stereotypy neurological distribution and superficial location), VAS > 4  
                **Exclusion criteria:** pain relating to spasticity  
                **Age:** mean age 44.8  
                **Gender:** women 11, men 8  
                **Pain type:** neuropathic pain  
                **Type of MS:** not reported |
| Interventions | **Treatment:** anodal tDCS, 2mA current  
                  **Control:** sham tDCS  
                  **Duration:** 5 consecutive daily simulation (20-minute sessions) |
| Outcomes | • VAS (Pain)  
            • VAS (Anxiety)  
            • SF-MPQ  
            • MSQOLS4  
            • BDI |
| Notes | **Funding:** none to declare  
         **Conflicts of interest:** none to declare |

**Risk of bias**
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<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Randomisation list generated by a computer software</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Undear risk</td>
<td>Allocation concealment not described</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>Patients and assessing physician were blinded to group allocation</td>
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<tr>
<td>All outcomes</td>
<td>Low risk</td>
<td>Patients and assessing physician were blinded to group allocation</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>None lost to follow up</td>
</tr>
<tr>
<td>All outcomes</td>
<td>Low risk</td>
<td>All outcomes in the review reported</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>No other bias detected</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
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</tr>
</tbody>
</table>

**Nazari 2016**

**Methods**
- Randomised controlled trial, single-blinded
- Study conducted in Iran
- Randomization through computer-generated lists
- Allocation concealment not described

**Participants**
- **Population source**: MS patients referred to the Clinic of Ayatollah Khashi Hospital (Isfahan, Iran) in 2014.
- **Numbers**: randomised 75; relaxation 25, reflexology 25, control 25
- **Inclusion criteria**: female, definite diagnosis of MS, 18-75 years of age, healthy body, not suffering from diseases other than MS, willing to participate in the study, not having a drug addiction, not being pregnant, not being medical staff, having chronic pain of at least one body organ, having a history of pain medication use, NRS = 4 for at least 6 months, expanded disability status scale of 0 to 7.5
- **Exclusion criteria**: receiving other complementary and alternative treatment during the study period, and reflexology treatment, receiving formal training and practicing reflexology in the previous 6 months, acute relapse 1 month preceding or during the study period, not wanting to continue their co-operation in the research
- **Age**: reflexology group (mean 34.4), relaxation (mean 33.9), control group (mean 34.4)
- **Gender**: female only
- **Type of MS**: relapsing remitting (reflexology 88%, relaxation 84%, control 80%)

**Interventions**
- **Treatment**: relaxation (audio tape guided relaxation), reflexology (general reflexology massage technique)
- **Control**: routine care 4 weeks

---

*Non-pharmacological interventions for chronic pain in multiple sclerosis (Review)*

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### Continued

**Outcomes**
- Pain (NRS)

**Notes**
- **Funding:** Research conducted under financial support of the Vice Chancellor for Research of Isfahan University of Medical Sciences
- **Conflicts of interest:** None to declare

### Risk of bias

<table>
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<tr>
<th>Bias</th>
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<th>Support for judgement</th>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Participants were randomly assigned, using minimisation method with MiniPy software</td>
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<td>Allocation concealment (selection bias)</td>
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<tr>
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<td>None lost to follow-up</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All outcomes reported</td>
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<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>The funding organisation(s) played no role in the study design, in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication</td>
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</tbody>
</table>

### Pali 2016

**Methods**
- Randomised controlled, cross-over, double-blinded trial
- Study conducted in France
- Randomisation method not discussed
- Allocation concealment not discussed

**Participants**
- **Population source:** MS patients recruited from inpatient and outpatient neurology departments at Henri Mondor hospital, Creteil, France
- **Numbers:** Randomised 16 (not reported number in each group)
- **Inclusion criteria:** Age 18-70 years of age, right-handedness as per Edinburgh Inventory, a definitive diagnosis of MS according to McDonalds Criteria, presence of neuropathic
pain as per neuropathic pain symptom inventory >3 months, VAS (0-100) > 40mm on a daily basis during a representative week, stable pharmacological and physical therapies since at least 1 month, the presence of measurable pain related evoked potentials at the right hand, the absence of MS relapses within the last 2 months and other neurological or psychiatric conditions.

Exclusion criteria: patients unable to perform the attention network test, deficits in visual fields or severe upper limb impairment based on medical research council scale score of < 12.

Age: mean age 47.4 years, age range 38-64 years

Gender: 13 women, 3 men

Type of MS: 11 relapsing remitting, 4 secondary progressive, 1 primary progressive

Pain type: neuropathic pain

Adverse effects: phaeochromocytoma (1 chlam), insomnia (6 chlam, 5 treatment), nausea (4 chlam, 2 treatment), headache (1 chlam)

| Interventions | Treatment: tRNS
| Control: sham controlled
| Duration: 3 daily consecutive sessions of sham or tRNS

| Outcomes | • VAS
| • BPI
| • ATN
| • HADS
| • VRFS
| • MRP
| • FMIA

| Notes | Funding: received grants
| Conflicts of interest: none

| Risk of bias | Authors' judgement | Support for judgement
| Random sequence generation (selection bias) | Unclear risk | Randomisation not discussed
| Allocation concealment (selection bias) | Unclear risk | Allocation concealment not described
| Blinding of participants and personnel (performance bias) | Low risk | Blinding was achieved
| All outcomes | | |
| Blinding of outcome assessment (detection bias) | Unclear risk | Blinding of assessment was not described, or if it was achieved
| All outcomes | | |
| Incomplete outcome data (attrition bias) | Low risk | None lost to follow-up
| All outcomes | | |
## Pain 2016 (Continued)

<table>
<thead>
<tr>
<th>Selective reporting (reporting bias)</th>
<th>Low risk</th>
<th>All outcomes reported</th>
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<tbody>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Received grants, not discussed if affected results</td>
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</tbody>
</table>

## Warte 2006

### Methods
- Randomised controlled trial, single-blinded
- Study conducted in Northern Ireland
- Randomisation through computer-generated lists
- Allocation concealment not described

### Participants
<table>
<thead>
<tr>
<th>Population source: recruited from MS hospital clinics and other clinics within Northern Ireland</th>
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<tbody>
<tr>
<td>Numbers: randomised 90, low frequency (4Hz) 30, high frequency (110Hz) 30, placebo 30</td>
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<tr>
<td>Inclusion criteria: 18-80 years, chronic (&gt;3 months), stable lumbar back pain, participants undergoing concurrent treatments and stable for 30 days before and throughout the duration of the trial</td>
</tr>
<tr>
<td>Exclusion criteria: comorbidity including serious spinal pathology or psychosocial risk factors, or both, acute MS relapses 1 month preceding or during the trial period, any contraindication to TENS, judged not competent to give informed consent, analgesic abuse, scapel pressure ulcers, participation in other research studies within the previous 3 months</td>
</tr>
<tr>
<td>Age: range 21-78 years, low frequency (mean 45.6), high frequency (mean 47.8), placebo (mean 48.7)</td>
</tr>
<tr>
<td>Gender: low frequency (24 women, 6 men), high frequency (22 women, 8 men), placebo 23 women, 7 men</td>
</tr>
<tr>
<td>Type of MS: not reported</td>
</tr>
<tr>
<td>Pain type: low back pain</td>
</tr>
</tbody>
</table>

### Interventions
<table>
<thead>
<tr>
<th>Treatment: low frequency (4Hz), high frequency (110Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control: placebo TENS</td>
</tr>
<tr>
<td>Duration: lumbar spine application, &gt;= twice daily application, 45 minutes for 6 weeks and anytime pain occurred</td>
</tr>
</tbody>
</table>

### Outcomes
<table>
<thead>
<tr>
<th>Primary</th>
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</thead>
<tbody>
<tr>
<td>VAS (Average)</td>
</tr>
<tr>
<td>MPQ</td>
</tr>
<tr>
<td>Secondary</td>
</tr>
<tr>
<td>VAS (Worst)</td>
</tr>
<tr>
<td>RMDQ</td>
</tr>
<tr>
<td>BI</td>
</tr>
<tr>
<td>RMI</td>
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<td>MSQOL54</td>
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### Notes
- Funding: financial support from MS Society of Great Britain and Northern Ireland
- Conflicts of interest: no other conflicts of interest listed
### Risk of bias

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<th>Authors’ judgement</th>
<th>Support for judgement</th>
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<td>Random sequence generation (selection bias)</td>
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<td>Randomisation was achieved using a computer-generated list</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Undecr risk</td>
<td>Allocation concealment not described</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>The frequencies set on the TENS units were masked and participants were blinded to the treatment group</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Low risk</td>
<td>Investigator allocating each unit to participants was blinded</td>
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<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>Five participants lost to follow-up</td>
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<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All outcomes reported</td>
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<tr>
<td>Other bias</td>
<td>Undecr risk</td>
<td>Did not describe if funding had impact on results</td>
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</table>


### Characteristics of excluded studies (ordered by study ID)

<table>
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<th>Study</th>
<th>Reason for exclusion</th>
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<tbody>
<tr>
<td>Ansimos 2016</td>
<td>Pain: not an outcome criteria</td>
</tr>
<tr>
<td>Backes 2016</td>
<td>Not a clinical controlled trial</td>
</tr>
<tr>
<td>Reference</td>
<td>Study Type</td>
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<tr>
<td>----------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Barlow 2009</td>
<td></td>
</tr>
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<td>Catena 2014</td>
<td></td>
</tr>
<tr>
<td>Dodelabadi 2012</td>
<td></td>
</tr>
<tr>
<td>Hasnipour-Dokordi 2015</td>
<td></td>
</tr>
<tr>
<td>Hasnipour-Dokordi 2016</td>
<td></td>
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<tr>
<td>Jensen 2007</td>
<td></td>
</tr>
<tr>
<td>Jensen 2011</td>
<td></td>
</tr>
<tr>
<td>Marinelli 2015</td>
<td></td>
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<tr>
<td>Mathiowetz 2005</td>
<td></td>
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<tr>
<td>McGuire 2015</td>
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<td>Negahban 2013</td>
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<td>Okan 2004</td>
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<td>Fhusti 2013</td>
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<td>Barall 2002</td>
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<td>Seada 2013</td>
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<tr>
<td>Smedal 2011</td>
<td></td>
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<tr>
<td>Storm 2006</td>
<td></td>
</tr>
<tr>
<td>Van der Linden 2013</td>
<td></td>
</tr>
</tbody>
</table>
APPENDICES

Appendix 1. 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 characterized by widespread pain, the cause is unknown
- **Hyperesthesia:** elevated 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’
- **Thermite phenomenon:** 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
- **Paresthesia:** a sudden occurrence or intensification of symptoms
- **Proprioception:** the perception of outside stimuli that indicates the body of the relative position of its parts
- **Psychogenic pain:** physical pain that is caused, increased, or prolonged by mental, emotional, or behavioral 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
- **Sensory neuron:** sensory system in the body involved in detecting touch, pressure, pain, temperature, movement and vibration
- **Therapeutic:** application of heat or cold to the body for pain relief
- **Toxic spasm:** sudden abnormal muscle contraction
- **Transcranial direct cortical stimulation:** non-invasive brain stimulation using low currents
- **Transcranial magnetic 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


Appendix 3. PsychINFO

S1 TX multiple sclerosis
S2 DE “Multiple Sclerosis”
S3 TX demyelinating disease
S4 DE “Demyelination”
S5 TX cranial 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”

Non-pharmacological interventions for chronic pain in multiple sclerosis (Review)
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 édème
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 dysesthesia or TX dysasthésie*
S16 S11 or S12 or S13 or S14 or S15
S17 (DE "PAIN INTRACTABLE")
S18 (DE "PAIN MEASUREMENT")
S19 (DE "PAIN THRESHOLD")
S20 TX nociceptors*
S21 AB pain N5 (refer* or refractory or intractable or receptor* or nociceptor* or musculoskeletal or chronic or intense* or threshold* or shoulder* or abdominal* or back or neuropath*)
S22 TI pain N5 (refer* or refractory or intractable or receptor* or nociceptor* or musculoskeletal or chronic or intense* or threshold* or shoulder* or abdominal* or back or neuropath*)
S23 (TI nociceptor* N5 neuron*) OR TI pain*
S24 S17 or S18 or S19 or S20 or S21 or S22 or S23
S25 S16 and S17 and S24

Appendix 5. MANTIS/Ovid
1 multiple sclerosis.mp.
2 multiple sclerosis.sh.
3 demyelinating disease*.mp.
4 demyelinating diseasessh.
5 transverse myelitis.mp
6 myelitis, transverse.sh.
7 neuromyelitis optica.mp
8 optic neuritis.mp
9 optic neuritis.sh

Non-pharmacological interventions for chronic pain in multiple sclerosis (Review)

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CONTRIBUTIONS OF AUTHORS
Bhaskar Amarya (BA) and Fay Khan (FK) were involved in all aspects of the protocol. All authors were involved at the review stage.

DECLARATIONS OF INTEREST
The review 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.

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

SOURCES OF SUPPORT

Internal sources

- Department of Rehabilitation Medicine, Royal Melbourne Hospital, Australia.
External sources

- None, Other.

Differences Between Protocol and Review

- A meta-analysis was not possible due to methodological, clinical and statistically heterogeneity of included studies
- Change of number of risk of bias items to include 'other bias' and 'blinding of outcome assessment'.
Observational study

Chronic pain in multiple sclerosis: A 10-year longitudinal study

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Department of Rehabilitation Medicine, Royal Melbourne Hospital, 34-54 Princes Rd Parkville, Melbourne, VIC 3052, Australia

Department of Medicine (Royal Melbourne Hospital), University of Melbourne, Melbourne, VIC, Australia

School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia

HIGHLIGHTS

- Over 10 years chronic pain in MS becomes more generalized and greater pain severity.
- There is deterioration in quality of life, chronic pain grade.
- There is impact on living arrangements and increased healthcare utilisation.
- Barriers to medications include fear of taking medications and side effects.

ARTICLE INFO

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Keywords:
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Chronic pain
Quality of life
Disability

ABSTRACT

Background and purpose: Pain is a common symptom associated with multiple sclerosis (MS), and has lasting effects on an individual’s functional capacity and quality of life. A wide range of prevalence rates of pain (between 23% and 93%) have been reported in MS and this is mainly due to the methodological differences amongst the studies such as variability in patient sources, method of sampling and the definition of pain used. Chronic pain in MS, defined as pain lasting for greater than 3–6 months, can have a significant impact on their biopsychosocial health, including negative impact on activities of daily living, relationships, and social participation. The long-term course of MS-related pain and its impact in an Australian cohort over a 10-year period has been investigated earlier. The aim of this longitudinal study was to describe the impact of chronic pain, pain-related disability and care burden in persons with MS over a 10-year period. The aim of this longitudinal study was to describe the impact of chronic pain, pain-related disability and care burden in persons with MS over a 10-year period.

Methods: This was a prospective longitudinal study conducted at the Rehabilitation Department of Royal Melbourne Hospital (RMH), a tertiary referral hospital in Victoria and Australia. The source of participants was from the RMH MS database and contains detailed MS patient information including demographic data, diagnosis details (using McDonald’s criteria), pain characteristics. Structured face-face interviews and validated measures were used, which include the visual analogue scale (VAS), chronic pain grade (CPG), the assessment of quality of life (AQoL) and the carer strain index (CSI). The mean age of the participants (n = 70) was 55.3 years and majority (70%) were female.

Results: The mean age of the participants (n = 70) was 55.3 years and majority (70%) were female. The findings show that over time (10 years), participants report having greater bilateral bodily pain and greater description of pain as “worse as it could be”. Pain types were similar to 7 years follow-up but remained higher than baseline. There was a significant deterioration in quality of life in those with more severe CPC over time. Almost half of the participants (31 [44%]) required care either from a private carer, institution or a family member. Although fear of taking medications and side effects were common barriers to treatment for pain, there was an increase in the use of pharmacological treatment over time and an increase in the use of healthcare services, mainly neurologists and general practitioners.

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1. Introduction

Pain is a common symptom associated with multiple sclerosis (MS) and has lasting effects on an individual's functional capacity and quality of life [1-3]. A wide range of prevalence rates of pain (between 23% and 90%) [4,5] have been reported in MS and this is mainly due to the methodological differences amongst the studies such as variability in patient sources, method of sampling, and the definition of pain used [3,6,7]. Chronic pain in MS, defined as pain lasting for greater than 3–6 months [8], can have a significant impact on their biopsychosocial health, including negative impact on activities of daily living, relationships, and social participation [2,9].

The long-term course of MS-related pain and its impact in an Australian cohort over a 7-year period has been investigated earlier. This longitudinal 7-year follow-up study conducted in a community cohort, showed that though average pain intensity did not change over time (at 7 years from baseline), more participants reported higher rates of pain and greater disability limiting their daily activities [1]. Further, there was deterioration in quality of life (QoL) and increased dependency due to pain-related disability. The authors also found that participants were using less pharmacological medication and using other non-conventional therapies, which is mainly due to barriers to access to healthcare services, lack of finances, and fear of side effects [9]. An Audy study by Adele et al. reported high prevalence of chronic pain and increased pain-related disability (44%) in a community cohort of MS [4]. Stewart et al. in another 5-year longitudinal study, found significant increase in the number of chronic and acute pain syndromes since diagnosis over time with deterioration in disability [10].

There is a high prevalence of chronic pain in MS which tends to increase over time. To date, there is a lack of longitudinal data on chronic pain in MS past 7 years [3,11] and more research is needed to inform clinical practice in regards to MS-related pain and its long-term impact on disability, functional activity, care stress, and environmental factors (such as living arrangements) [3,6,12]. The objective of this study was to examine longer term effects of chronic pain over 10 years in MS in the community and assess the pain-related disability, care burden, healthcare utilization, and management strategies.

2. Methods

2.1. Setting

This was a prospective longitudinal study conducted at the Rehabilitation Department of Royal Melbourne Hospital (RMH), a tertiary referral hospital in Victoria and Australia. The source of participants was from the RMH MS database and contains detailed MS patient information including demographic data, diagnosis details (using McDonald’s criteria [13]), pain characteristics, pain severity, and management. This study was approved by the Melbourne Health Human Research and Ethics Committee (HREC 2016.1221). The profile of patients captured by the RMH MS database is described elsewhere [3,11]. A pilot evaluation of pain outcomes of persons with MS at the RMH was published in 2005 (n = 101) and further 7-year follow-up study of this cohort (n = 74) for long-term outcomes was published in 2011 [5].

2.2. Participants

The participants for the present study were recruited from an initial cohort of MS participants from the RMH MS database in 2005 (n = 101) [11]. The inclusion criteria for the study were: >18 years of age, fulfilled McDonald’s diagnostic criteria [13,14] and had chronic pain defined as (constant or intermittent) pain experienced every day for greater than or equal to 3 months in the 6 months before the interview [10].

The exclusion criteria included: participants with significant comorbidities (medical instability due to brittle diabetes or anemia) or unstable psychiatric disorders, patients with acute pain and/or who did not fulfill the criterion of chronic pain. Caregiver for this study was defined as a person who lives with the participant with MS and provides them with the most care and assistance [15-17].

2.3. Procedure

All eligible patients in the database who participated in the longitudinal study in 2013 were contacted by phone, invited to participate in the study, and were then assessed by an independent assessor. A face-to-face structured interview technique was used, which was conducted by an independent trained research officer using a structured format and standardized instruments (see Measures). All interviews took approximately 45 min and were based in the community setting and home visits. The assessor did not provide prompts but did provide assistance for those who had difficulty answering the questionnaire. Appropriate rest breaks were also provided during these interview sessions. All assessments were secured and entered into the database by an independent data entry officer.

2.4. Measurements

All measurement tools used in the baseline and 7-year follow-up study in 2013 were used for this study. These included pain assessment by using temporal criteria (chronic) as well as a symptom-orientated approach using a structured questionnaire and interview [3]. All reported pain that fulfilled the study criteria...
was included, incorporating neuropathic and nociceptive types [17,18].

2.5. Multiple sclerosis related measures

MS-related information collected included the participant demographic details and information about MS symptom onset and diagnosis obtained from the RMH Rehabilitation database.

2.6. Pain measures

These included in the last 6 months: location of pain, descriptive pain intensity, duration of pain (in years), temporal aspects of pain and trigger factors. Types of pain were categorized to neuropathic pain (characterized by burning, numminess, itching, pricking, allodynia and hyperalgesia) and nociceptive pain (characterized by aching, dull, stabbing, throbbing, squeezing, cramping and pain on movement) using descriptors. Participants could have characteristics of neuropathic and nociceptive pain. Other types of pain included trigeminal neuralgia, painful spasm and back pain and headache to be consistent with previous 7-year longitudinal study [3]. Information in regards to pharmacological pain treatment was collected by listing the medications used (current and past 6 months) and classified using categories from the monthly index of medical specialties Australia [30]. The participants were also asked about their usual pain management across the categories of medication, physical/mechanical/temperature manipulation, rest/sleep exercise, distraction or alternative techniques. Other information on perceived barriers and access to healthcare services (medical practitioners, allied health and alternative health practitioners) in the last 12 months were also collected [30].

2.7. Visual analogue scale (VAS)

The VAS, a unidimensional measurement of pain intensity across a continuum of which, was used to access the pain intensity. It is quick and easy to administer and widely used in adult populations. It was asked on average relating to the last 6 months as was used in the previous 7-year follow-up study.

2.8. Simple descriptive pain scale

The simple descriptive pain scale, a unidimensional measurement, was used to access the pain descriptors (no pain, mild pain, moderate pain, severe pain, very severe pain and worst possible pain) [21].

2.9. Chronic pain grade (CPG)

The CPG, a multidimensional measure, evaluated 2 dimensions of chronic pain: pain intensity and pain related disability. These sub-scores were combined to calculate a CPG from 0 to 100 Grade I (low disability–low intensity), Grade II (low disability–high intensity), Grade III (high disability–moderately limiting), and Grade IV (high disability–severely limiting) [18].

2.10. The assessment of quality of life (AQoL)

The AQoL was used to assess health-related quality of life in four domains: independent, social relations, physical senses and psychological well-being. AQoL has been validated in a range of patient groups [35].

<table>
<thead>
<tr>
<th>MS Database 2005</th>
<th>2005 (N=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insufficient information 2</td>
<td>Unavailable for interview 1</td>
</tr>
<tr>
<td>withdrew from study 2</td>
<td>Total participants = 95</td>
</tr>
</tbody>
</table>

| Did not meet criteria for chronic pain | (N=9) |
| Not able to be contacted | (N=17) |

Fig. 1: Flowchart of recruitment process.

2.11. Care strain index (CSI)

The CSI is a 13-item tool that describes stressful aspects of caregiving. The caregiver indicated how stressful each identified item was through ‘yes’ and ‘no’ responses. A score of 27 out of 13 indicates caregiver stress [15,18].

2.12. Data analysis

All analyses performed were consistent with the procedures adopted in the previous baseline and 7-year follow-up study [3]. Descriptive statistics described the prevalence and characteristics of pain, utilization of health care, perceived barriers to treatment and pain management techniques and carer strain. Due to the small group size and the skewed distribution, non-parametric statistical analyses (Kruskal–Wallis test) was used to compare patients through various CPG. The AQoL utility scores were calculated according to published guidelines and the Wilcoxon signed-rank test was used to compare AQoL scores between the 7-year and 10-year follow-ups. All calculations were performed using IBM SPSS for Windows version 22.0 and statistical significance was determined by a level of <0.05.

3. Results

Of the 74 participants assessed to have chronic pain based on the aforementioned definitions, 70 participants were recruited for this 10-year longitudinal study. Four participants were unable to be contacted. The recruitment process is shown in Fig. 1.

The mean age of the participants was 59.8 ± 9 years (range 35–74 years) and the majority (70%) were female. Mean disease duration since MS diagnosis was 19.5 years (range 15–25 years) and all participants had the progressive MS type which is expected given the participant’s disease duration. At 16-year follow-up, 31 (44%) participants were either living with a private carer, a family member who is a carer or in a high-care (nursing home) facility, whereas every participant was still living at home at 7-year follow-up (Table 1).
Table 1: Sociodemographic characteristics of participants (n = 79).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>7 year follow up n = 15 (unless otherwise stated)</th>
<th>10 year follow up n = 15 (unless otherwise stated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) [mean (SD); range]</td>
<td>51.6 (13.7); 35–71</td>
<td>59.8 (8.0); 38–74</td>
</tr>
<tr>
<td>Sex female</td>
<td>51 (71.6)</td>
<td>48 (78)</td>
</tr>
<tr>
<td>Living alone</td>
<td>41 (57.0)</td>
<td>19 (31.0)</td>
</tr>
<tr>
<td>Partner/family</td>
<td>19 (24.7)</td>
<td>0</td>
</tr>
<tr>
<td>Career (private, family, institution)</td>
<td>46 (62.2)</td>
<td>6 (97)</td>
</tr>
<tr>
<td>Disease duration</td>
<td>18.0 (12.2)</td>
<td>18.5 (13.5)</td>
</tr>
<tr>
<td>MS type</td>
<td>9 (12.2)</td>
<td>9 (13)</td>
</tr>
<tr>
<td>Relapsing remitting</td>
<td>9 (12.2)</td>
<td>9 (13)</td>
</tr>
<tr>
<td>Secondary progressive</td>
<td>48 (62.2)</td>
<td>6 (97)</td>
</tr>
<tr>
<td>Primary progressive</td>
<td>9 (12.2)</td>
<td>9 (13)</td>
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</table>

Table 2: Characteristics and descriptors of chronic pain intensity and frequency.

<table>
<thead>
<tr>
<th>Location</th>
<th>Baseline n = 79</th>
<th>7 year follow up n = 79</th>
<th>10 year follow up n = 79</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head-unilateral</td>
<td>7 (11.5)</td>
<td>8 (12.0)</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Head-bilateral</td>
<td>10 (16.4)</td>
<td>12 (16.4)</td>
<td>20 (38.5)</td>
</tr>
<tr>
<td>Limb-upper-unilateral</td>
<td>13 (21.3)</td>
<td>18 (24.3)</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Limb-lower-unilateral</td>
<td>8 (13.1)</td>
<td>7 (9.3)</td>
<td>18 (35.3)</td>
</tr>
<tr>
<td>Limb-lower-unilateral</td>
<td>11 (16.0)</td>
<td>15 (19.5)</td>
<td>7 (15.6)</td>
</tr>
<tr>
<td>Limb-bilateral</td>
<td>26 (42.0)</td>
<td>39 (52.2)</td>
<td>65 (142)</td>
</tr>
<tr>
<td>Trunk-unilateral</td>
<td>8 (13.1)</td>
<td>12 (16.2)</td>
<td>2 (28)</td>
</tr>
<tr>
<td>Trunk-bilateral</td>
<td>20 (32.8)</td>
<td>16 (21.4)</td>
<td>28 (46)</td>
</tr>
<tr>
<td>Descriptiv pain intensity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>17 (27.7)</td>
<td>24 (32.4)</td>
<td>23 (26.5)</td>
</tr>
<tr>
<td>Moderate</td>
<td>33 (54.1)</td>
<td>29 (37.2)</td>
<td>16 (18.3)</td>
</tr>
<tr>
<td>Severe</td>
<td>5 (8.2)</td>
<td>16 (21.6)</td>
<td>17 (19.7)</td>
</tr>
<tr>
<td>Very severe</td>
<td>2 (3.2)</td>
<td>3 (4.1)</td>
<td>2 (28)</td>
</tr>
<tr>
<td>Where pain possible</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumbar</td>
<td>5 (7.9)</td>
<td>11 (14.4)</td>
<td>13 (15.5)</td>
</tr>
<tr>
<td>Types of pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dorsalalgia</td>
<td>37 (54.7)</td>
<td>36 (46.2)</td>
<td>18 (34.3)</td>
</tr>
<tr>
<td>Neuropathic</td>
<td>4 (6.0)</td>
<td>6 (8.0)</td>
<td>21 (40.3)</td>
</tr>
<tr>
<td>Trigeminal neuralgia</td>
<td>4 (6.6)</td>
<td>8 (10.3)</td>
<td>7 (15.6)</td>
</tr>
<tr>
<td>Facial pains and back pain</td>
<td>33 (54.3)</td>
<td>27 (34.3)</td>
<td>28 (49)</td>
</tr>
<tr>
<td>Headache</td>
<td>13 (21.3)</td>
<td>7 (9.3)</td>
<td>7 (15.6)</td>
</tr>
<tr>
<td>VAS (mean)</td>
<td>5.3</td>
<td>5.2</td>
<td>5.2</td>
</tr>
</tbody>
</table>

Table 3: Pain management techniques used by participants with chronic pain.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Baseline n = 79</th>
<th>7 year follow up n = 79</th>
<th>10 year follow up n = 79</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesics-opioids</td>
<td>33 (54.1)</td>
<td>31 (47.5)</td>
<td>31 (47.5)</td>
</tr>
<tr>
<td>Analgesics-antidepressants</td>
<td>4 (6.5)</td>
<td>4 (5.6)</td>
<td>11 (15.7)</td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td>11 (18.0)</td>
<td>7 (9.3)</td>
<td>7 (10)</td>
</tr>
<tr>
<td>Muscle relaxants and anticonvulsants</td>
<td>18 (29.5)</td>
<td>17 (23)</td>
<td>38 (40)</td>
</tr>
<tr>
<td>Antidepressants and antidepressants</td>
<td>18 (29.5)</td>
<td>20 (27)</td>
<td>26 (27)</td>
</tr>
</tbody>
</table>

3.2. Management techniques

At 10-year follow-up, there were more participants using medications compared to 7-year follow-up. There was an increase in the number of participants using non-opioids, epidid, muscle relaxants, antidepressants, and anticonvulsants (except anti-inflammatories) but not to the extent at baseline (Table 3). The most common analgesics used were non-derivatives 54 (44.3%) and the most common non-pharmacological intervention was physical-electrical 45 (54.3%) which included massage, hydrotherapy, change in position and transcutaneous electrical nerve stimulation. There was similar use of non-pharmacological interventions in the 10-year follow-up compared to 7-year follow-up.

3.3. Healthcare utilization

There was an increase in the use of health professionals at the 10-year follow-up. The two main practitioners were general practitioners and neurologists (61 (87.1%) and 66 (85.7%) respectively) compared to 40 (54.1%) and 46 (62.2%) respectively at the 7-year follow-up. However there were still less participants utilizing rehabilitation and pain specialists. There were more patients reporting side-effects 5 (7.1%) and being fearful of taking medications 10 (14.3%). These were considered barriers to accessing pharmacological treatments. Other barriers, such as environmental and cognitive barriers were similar at the two time-points.

3.4. Quality of life measures

At the 10-year follow-up QoL of the participants deteriorated significantly, particularly in the following domains: illness (p < 0.001) independent living (p = 0.001), social relationships (p < 0.001) and physical senses (p < 0.001). This suggests that participants were now more dependent. Interestingly, there were no statistically significant changes in the psychological well-being domain, suggesting that many had adapted to the lifestyle and circumstances. The GDSmean was 5.4 but in 6/13 cases the GDS score was 7 or higher which represented significant care stress either through pain or other MS-related symptoms [17].

3.5. Chronic pain grade

The CPC classified chronic pain severity, based on scores for items on pain intensity and pain-related disability. There were similar scores on the CPC between the 16-year and 7-year follow-up periods, but more participants had progressed to higher CPC III 7 (10%) and CPC IV 14 (20%) suggesting greater pain-related disability.

4. Discussion

This prospective longitudinal study showed that in a 10-year time-period, 70 participants had chronic pain. A significant
proportion of participants had developed greater bilateral body pain involving the trunk and limbs. However, there was no greater pain types compared to 7-year follow-up and there was greater reporting of pain as severe as it could be over time. This suggests that although the mean pain score remains the same as previous time points there were now more people describing greater pain subjectively suggesting a greater emotional component to their chronic pain. These findings were different to the 5-year longitudinal study where there was an increase in chronic pain syndromes. However, there were methodological differences including the listing of specific pain locations, the use of acute and chronic syndromes and neuropathic and nociceptive definitions [10].

Types of pain, mean pain scores and pain descriptors remained similar throughout the time periods. The similarity in mean pain scores over time could be explained by a phenomenon known as ‘response shift’ [22,23]. This phenomenon is a re-conceptualization of the impact of a chronic disease over time and these changes reflect the adaptation or accommodation for an illness or chronic condition and should be taken into consideration for longitudinal studies [22,23]. This has implications on measurement properties and outcome measures [17]. Given that there is a high prevalence of chronic pain in neurological conditions, neurologists still rank treating chronic pain as low [14]. However, in this study the most common health professionals involved in their care were neurologists and general practitioners but there was limited consultation with pain and rehabilitation specialists.

This study cannot comment on the development of widespread pain as the previous 7-year longitudinal study did not define this term. Widespread pain is defined in the literature as pain on the left side of the body, right side of the body, above the waist, below the waist and axial skeleton [24]. There is limited evidence on the pathophysiology of chronic pain and the development of widespread pain in MS which is based on other chronic pain states [25]. However, previous studies have shown that individuals with chronic pain distress can go on to develop chronic widespread pain [26,27]. Postulated mechanisms include central sensitization which can develop in individuals from a repetitive noxious source that produces an expansion of receptive fields and hyperalgesia [27,28]. Fibromyalgia-type symptoms were also common in MS patients and higher than the general population. An explanation is sharing the female sex as a risk factor which is common in both conditions [29]. Central sensitization mechanisms include long term potentiation, altered descending inhibitory systems and a change in signaling pathways and synaptic plasticity [30,31]. Other mechanisms of chronic pain may include inadequate modulation of sensory processing, posture and neuropathic mechanisms which include deafferentation and upregulation in neuroinflammation in the dorsal root ganglion [25,32,33].

Treatment of chronic pain in MS is difficult and there is a paucity of evidence for the effectiveness of pharmacological and non-pharmacological treatments. Common pharmacological treatments include tricyclic antidepressants and gabapentinoids [34] but there is a lack of evidence for non-pharmacological treatments which may be important for future therapy. Barriers to treatment include fear of taking medications and side-effects [3,4]. Despite these barriers to pharmacological treatment, participants used more medications over time in this study. This phenomenon could be explained by ongoing prescription by medical practitioners, highlighting the importance of reviewing medications for their effectiveness and cessation of medications that do not benefit. This study highlights the need for increased awareness of medication safety, poly-pharmacy and prescribing errors, supported by a literature review of medication safety in Australia [35].

As expected there was a progression of disease and to more severe pain grade with deterioration in AQOL scores. This deterioration was manifested clinically by increased dependence and greater pain-related disability, and was associated with a significant percentage of patients who now required care from another individual, carer or institution [11,44]. Caregivers are vital in maintaining people with MS in the community and caregiver strain is associated with increased caregiver burden and decreased quality of life [15,17]. Although only 13 participants identified as having a carer, more than half of the carers complained of sleep disturbance, incontinence, physical strain, family and personal constraints. The results of this study were similar to other reports with demands on personal plan, emotional adjustments and sleep disturbance [16,17].

The strengths of this longitudinal follow-up study include: retention of a large proportion of the original participants, ensuring a definitive diagnosis of MS, standardized definition of pain and collection of information through face-to-face interviews. The limitations of the study include a relatively small sample size and potential sampling bias; although participant demographics were similar to other MS prevalence studies [33,36]. Other limitations include not having a control group and all findings being correlational and probably not fully representing the impact of chronic pain due to other factors in daily activities and psychology. MS patients without pain were not included in the study, as this was a criteria in the 7-year follow-up study, which did not allow for a comparison with those with no pain and to the length of time of MS diagnosis only secondary progressive and primary progressive MS types were involved. The use of descriptors for classifying neuropathic and nociceptive pain types is another limitation of the study as participants may have descriptors representative of both types. Use of the term mixed pain relating to different pains through different pathophysiological mechanisms that have nociceptive and neuropathic components [3] may be more beneficial. However, in order to be consistent and for comparison with the previous 7-year follow-up longitudinal study this classification system was retained [2]. Unlike the previous study, this longitudinal study included participants residing in institutions, which may result in an over-representation of pain and disability compared to the previous study. However, these participants were also present in 7-year follow-up and it is important to note their progression to institutions, increased care needs and costs.

5. Conclusion

This study shows that there is an increased need to be aware of chronic pain in MS and treatment is difficult despite the use of multiple treatment modalities as pain quality, intensity and location changes over time. Physicians should be encouraged to consider pain and treat pain given its potential to cause limitation in activity, lower quality of life and increase carer stress and burden [2,16,25].

Ethical issues

None to declare.

Conflicts of interest

The authors have no conflicts of interest to report.

Acknowledgements

We thank all the participants in this study.

References

Appendix 2. Questionnaires

Kurtzke Functional Systems Scores (FSS)

Pyramidal Functions
0 - Normal
1 - Abnormal signs without disability
2 - Minimal disability
3 - Mild to moderate paraparesis or hemiparesis (detectable weakness but most function sustained for short periods, fatigue a problem); severe monoparesis (almost no function)
4 - Marked paraparesis or hemiparesis (function is difficult), moderate quadriparesis (function is decreased but can be sustained for short periods); or monoplegia
5 - Paraplegia, hemiplegia, or marked quadriparesis
6 - Quadriplegia
9 - (Unknown)

Cerebellar Functions
0 - Normal
1 - Abnormal signs without disability
2 - Mild ataxia (tremor or clumsy movements easily seen, minor interference with function)
3 - Moderate truncal or limb ataxia (tremor or clumsy movements interfere with function in all spheres)
4 - Severe ataxia in all limbs (most function is very difficult)
5 - Unable to perform coordinated movements due to ataxia
9 - (Unknown)

Record #1 in small box when weakness (grade 3 or worse on pyramidal) interferes with testing.

Brainstem Functions
0 - Normal
1 - Signs only
2 - Moderate nystagmus or other mild disability
3 - Severe nystagmus, marked extraocular weakness, or moderate disability of other cranial nerves
4 - Marked dysarthria or other marked disability
5 - Inability to swallow or speak
9 - (Unknown)
**Sensory Function**

0 - Normal
1 - Vibration or figure-writing decrease only in one or two limbs
2 - Mild decrease in touch or pain or position sense, and/or moderate decrease in vibration in one or two limbs; or vibratory (c/s figure writing) decrease alone in three or four limbs
3 - Moderate decrease in touch or pain or position sense, and/or essentially lost vibration in one or two limbs; or mild decrease in touch or pain and/or moderate decrease in all proprioceptive tests in three or four limbs
4 - Marked decrease in touch or pain or loss of proprioception, alone or combined, in one or two limbs; or moderate decrease in touch or pain and/or severe proprioceptive decrease in more than two limbs
5 - Loss (essentially) of sensation in one or two limbs; or moderate decrease in touch or pain and/or loss of proprioception for most of the body below the head
6 - Sensation essentially lost below the head
9 - (Unknown)

**Bowel and Bladder Function**

(Rate on the basis of the worse function, either bowel or bladder)

0 - Normal
1 - Mild urinary hesitance, urgency, or retention
2 - Moderate hesitance, urgency, retention of bowel or bladder, or rare urinary incontinence (intermittent self-catheterization, manual compression to evacuate bladder, or finger evacuation of stool)
3 - Frequent urinary incontinence
4 - In need of almost constant catheterization (and constant use of measures to evacuate stool)
5 - Loss of bladder function
6 - Loss of bowel and bladder function
9 - (Unknown)
Visual Function
0 - Normal
1 - Scoloma with visual acuity (corrected) better than 20/30
2 - Worse eye with scotoma with maximal visual acuity (corrected) of 20/30–20/59
3 - Worse eye with large scotoma, or moderate decrease in fields, but with maximal visual acuity (corrected) of 20/60–20/99
4 - Worse eye with marked decrease of fields and maximal visual acuity (corrected) of 20/100–20/200; grade 3 plus maximal acuity of better eye of 20/60 or less
5 - Worse eye with maximal visual acuity (corrected) less than 20/200; grade 4 plus maximal acuity of better eye of 20/60 or less
6 - Grade 5 plus maximal visual acuity of better eye of 20/60 or less
9 - (Unknown)

Record #1 in small box for presence of temporal pallor

Cerebral (or Mental) Functions
0 - Normal
1 - Mood alteration only (does not affect EDSS score)
2 - Mild decrease in mentation
3 - Moderate decrease in mentation
4 - Marked decrease in mentation (chronic brain syndrome – moderate)
5 - Dementia or chronic brain syndrome – severe or incompetent
9 - (Unknown)
Kurtzke Expanded Disability Status Scale (EDSS)

- **0.0** - Normal neurological exam (all grade 0 in all Functional System (FS) scores*).
- **1.0** - No disability, minimal signs in one FS (i.e., grade 1).
- **1.5** - No disability, minimal signs in more than one FS (more than 1 FS grade 1).
- **2.0** - Minimal disability in one FS (one FS grade 2, others 0 or 1).
- **2.5** - Minimal disability in two FS (two FS grade 2, others 0 or 1).
- **3.0** - Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three or four FS grade 2, others 0 or 1) though fully ambulatory.
- **3.5** - Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3 (others 0 or 1) or five grade 2 (others 0 or 1).
- **4.0** - Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combination of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 500 meters.
- **4.5** - Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 300 meters.
- **5.0** - Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (e.g., to work a full day without special provisions); (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0).
- **5.5** - Ambulatory without aid for about 100 meters; disability severe enough to preclude full daily activities; (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combination of lesser grades usually exceeding those for step 4.0).
- **6.0** - Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting; (Usual FS equivalents are combinations with more than two FS grade 3+).
Graded Chronic Pain Scale (GCPS)

1. How would you rate your facial pain on a 0 to 10 scale at the present time, that is right now, where 0 is “no pain” and 10 is “pain as bad as could be”? 

<table>
<thead>
<tr>
<th>No pain</th>
<th>Pain as bad as could be</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td></td>
</tr>
</tbody>
</table>

2. In the past six months, how intense was your worst pain, rated on a 0 to 10 scale where 0 is “no pain” and 10 is “pain as bad as could be”? 

<table>
<thead>
<tr>
<th>No pain</th>
<th>Pain as bad as could be</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td></td>
</tr>
</tbody>
</table>

3. In the past six months, on the average, how intense was your pain rated on a 0-10 scale where 0 is “no pain” and 10 is “pain as bad as could be”? (That is you usual pain at times you were experiencing pain). 

<table>
<thead>
<tr>
<th>No pain</th>
<th>Pain as bad as could be</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td></td>
</tr>
</tbody>
</table>

4. In the past six months, how much has facial pain interfered with your daily activities rated on a 0 to 10 scale where 0 is “no interference” and 10 is “unable to carry on any activities”? 

<table>
<thead>
<tr>
<th>No interference</th>
<th>Unable to carry on any activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td></td>
</tr>
</tbody>
</table>

5. In the past six months, how much has facial pain changed your ability to take part in recreational, social and family activities where 0 is “no change” and 10 is “extreme change”? 

<table>
<thead>
<tr>
<th>No change</th>
<th>Extreme change</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td></td>
</tr>
</tbody>
</table>

6. In the past six months, how much has facial pain changed your ability to work (including housework) where 0 is “no change” and 10 is “extreme change”? 

<table>
<thead>
<tr>
<th>No change</th>
<th>Extreme change</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td></td>
</tr>
</tbody>
</table>

7. About how many days in the last six months have you been kept from your usual activities (work, school or housework) because of facial pain? 

---

Days
Scoring Criteria for Grading Chronic Pain Severity

*Characteristic Pain Intensity* is a 0 to 100 score derived from Questions 1 through 3:
   Mean (Pain Right Now, Worst Pain, Average Pain) X 10

*Disability Score* is 0 to 100 score derived from Questions 4 through 6:
   Mean (Daily Activities, Social Activities, Work Activities) X 10

*Disability Points:* Add the indicated points for Disability Days (Question 7) and for Disability Score.

### Disability Points

<table>
<thead>
<tr>
<th>Disability Days (0-180 Days)</th>
<th>Disability Score (0-100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 Days</td>
<td>0-29</td>
</tr>
<tr>
<td>7-14 Days</td>
<td>30-49</td>
</tr>
<tr>
<td>15-30 Days</td>
<td>50-69</td>
</tr>
<tr>
<td>31+ Days</td>
<td>70+</td>
</tr>
<tr>
<td>0 Points</td>
<td>0 Points</td>
</tr>
<tr>
<td>1 Point</td>
<td>1 Point</td>
</tr>
<tr>
<td>2 Points</td>
<td>2 Points</td>
</tr>
<tr>
<td>3 Points</td>
<td>3 Points</td>
</tr>
</tbody>
</table>

### Classification

**Grade 0**
- No TMD pain in prior 6 months

**Grade 1**
- Low Intensity: *Characteristic Pain Intensity* < 50
- Low Disability: < 3 Disability Points

**Grade II**
- High Intensity: *Characteristic Pain Intensity* ≥ 50
- Low Disability: < 3 Disability Points

**Grade III**
- High Disability: 3 to 4 Disability Points
- Moderately Limiting: (Regardless of *Characteristic Pain Intensity*)

**Grade IV**
- High Disability: 5 to 6 Disability Points
- Severely Limiting: (Regardless of *Characteristic Pain Intensity*)
Caregiver Strain Index (CSI)

I am going to read a list of things that other people have found to be difficult. **Would you tell me whether any of these apply to you?** (Give Examples)

<table>
<thead>
<tr>
<th>Experience</th>
<th>Yes = 1</th>
<th>No = 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep is disturbed (e.g., because it is in and out of bed or wanders around at night)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>It is inconvenient (e.g., because helping takes so much time or it’s a long drive over to help)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>It is a physical strain (e.g., because of lifting in and out of a chair; effort or concentration is required)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>It is confining (e.g., helping restricts free time or cannot go visiting)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>There have been family adjustments (e.g., because helping has disrupted routine; there has been no privacy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>There have been changes in personal plans (e.g., had to turn down a job; could not go on vacation)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>There have been emotional adjustments (e.g., because of severe arguments)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Some behavior is upsetting (e.g., because of incontinence; . . . has trouble remembering things; or . . . accuses people of taking things)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>It is upsetting to find . . . has changed so much from his/her former self (e.g., he/she is a different person than he/she used to be)</td>
<td></td>
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</tr>
<tr>
<td>There have been work adjustments (e.g., because of having to take time off)</td>
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<tr>
<td>It is a financial strain</td>
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<tr>
<td>Feeling completely overwhelmed (e.g., because of worry about . . . ; concerns about how you will manage)</td>
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</tr>
</tbody>
</table>

**Total Score** (Count yes responses. Any positive answer may indicate a need for intervention in that area. A score of 7 or higher indicates a high level of stress.)
# REFERRAL QUESTIONNAIRE

## Section 1 – Your details

<table>
<thead>
<tr>
<th>Title</th>
<th>Mr</th>
<th>Mrs</th>
<th>Ms</th>
<th>Miss</th>
<th>Family name (surname)</th>
<th>Given name(s)</th>
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<td>Country of Birth</td>
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<td>New Zealand</td>
<td>Other (please specify):</td>
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</tr>
<tr>
<td>Do you require an interpreter?</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If you answered yes, please specify the language:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are you hearing or sight impaired?</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you require help with written or spoken communication?</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (in cm):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (in kg):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are you of Aboriginal or Torres Strait Islander origin? (more than one may be ticked):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Yes, Aboriginal</td>
<td>Yes, Torres Strait Islander</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you ever served in the Australian Defence Force?</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are you a client of the Department of Veterans’ Affairs or have you received a benefit or support from the Department of Veterans’ Affairs?</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is there a compensation case relating to this episode?</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(If yes, record the type of compensation):</td>
<td>Worker’s Compensation</td>
<td>Public Liability</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor Vehicle</td>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How did your main pain begin?</td>
<td>Injury at home</td>
<td>Motor vehicle crash</td>
<td>After surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury at work/school</td>
<td>Cancer</td>
<td>No obvious cause</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury in another setting</td>
<td>Medical condition other than cancer</td>
<td>Other (please specify)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How long has your main pain been present? (Tick one box only):</td>
<td>Less than 3 months</td>
<td>12 months to 2 years</td>
<td>More than 5 years</td>
<td></td>
<td></td>
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<tr>
<td>3 to 12 months</td>
<td>2 to 5 years</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Which statement best describes your pain? *(Tick one box only)*

- □ Always present (always the same intensity)
- □ Always present (level of pain varies)
- □ Often present (pain free periods last less than 6 hours)
- □ Occasionally present (pain occurs once to several times per day, lasting up to an hour)
- □ Rarely present (pain occurs every few days or weeks)

Do you have any of the following?

- □ A mental health condition, in particular: □ PTSD  □ Anxiety  □ Depression
  Other *(please specify)* ..........................................................
- □ Arthritis *(including Rheumatoid/Osteoarthritis)*
- □ Muscle, bone and joint problems *other than arthritis* *(including Osteoporosis, Fibromyalgia)*
- □ Heart and circulation problems *(including Heart Disease, Pacemaker, Blood Disease)*
  In particular specify if you have: □ High Blood Pressure  □ High Cholesterol
- □ Diabetes
- □ Digestive problems *(including IBS, GORD, Stomach Ulcers, Reflux, Bowel Disease)*
- □ Respiratory problems *(including Asthma, Lung Disease, COPO, Sleep Apnoea)*
- □ Neurological problems *(including Stroke, Epilepsy, Multiple Sclerosis, Parkinson’s Disease)*
- □ Cancer
- □ Liver, kidney and pancreas problems *(including Pancreatitis, Kidney Disease)*
- □ Thyroid problems *(including Hyperactive or Hypoactive Thyroid, Graves’ Disease)*
- □ Any other medical conditions *(please specify)* ..........................................................

Health care *(other than your visits to the pain clinic)*

1. How many times in the past 3 months have you seen a general practitioner in regard to your pain? .......... times
2. How many times in the past 3 months have you seen a medical specialist *(e.g. orthopaedic surgeon)* in regard to your pain? .......... times
3. How many times in the past 3 months have you seen health professionals other than doctors *(e.g. physiotherapist, chiropractor, psychologist)* in regard to your pain? .......... times
4. How many times in the past 3 months have you visited a hospital emergency department in regard to your pain? *(Include all visits, regardless of whether or not you were admitted to the hospital from the emergency department)* .......... times
5. How many times in the past 3 months have you been admitted to hospital as an inpatient because of your pain? .......... times
6. How many diagnostic tests *(e.g. X-rays, scans)* have you had in the last 3 months relating to your pain? .......... tests
Section 2 - Your work

Are you currently employed (working for pay)?
☐ Yes - If yes, are you:  ☐ No - If no, are you:
☐ Working full-time  ☐ Unable to work due to a condition other than pain
☐ Working part-time  ☐ Unable to work due to pain
☐ Not working by choice (student, retired, homemaker)  ☐ Not working by choice (student, retired, homemaker)
☐ Seeking employment (I consider myself able to work but cannot find a job)

Please answer the questions below

During the past seven days, how many hours did you miss from work because of problems associated with your pain?
(include hours you missed on sick days, times you went in late, left early, etc. because of your pain. Do not include time you missed to attend this pain clinic).

During the past seven days, how many hours did you actually work?
(If 0 skip the next question and go to Section 3)

During the past seven days, how much did your pain affect your productivity while you were working?
Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual.

If pain affected your work only a little, choose a low number. Choose a high number if pain affected your work a great deal.

Consider only how much pain affected productivity while you were working

<table>
<thead>
<tr>
<th>Pain had no effect on my work</th>
<th>Pain completely prevented me from working</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td></td>
</tr>
</tbody>
</table>

CIRCLE A NUMBER
Section 3 – Medication use

Are you taking any medications?

☐ No *(please go to Section 4)*

☐ Yes *(Please list all the medications you are taking. Include both prescription and over-the-counter medicines)*

<table>
<thead>
<tr>
<th>Medicine name (as on the label)</th>
<th>Medicine strength (as on the label)</th>
<th>How many do you take per day?</th>
<th>How many days per week do you take this medication?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

*Referral Questionnaire – Adult, AUS v2.0*
Section 4 – Pain intensity and interference

On the diagram below, shade in ALL the areas where you feel pain.

On the diagram below, put an X on the ONE area that hurts most.
### Please rate your pain by circling the one number that best describes the following:

<table>
<thead>
<tr>
<th>Question</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Your pain at its worst in the last week?</td>
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<tr>
<td>2. Your pain at its least in the last week?</td>
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<tr>
<td>3. Your pain on average?</td>
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<tr>
<td>4. How much pain do you have right now?</td>
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</tbody>
</table>

### During the past week, how much has pain interfered with the following:

<table>
<thead>
<tr>
<th>Question</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Your general activity?</td>
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<tr>
<td>2. Your mood?</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>3. Your walking ability?</td>
<td></td>
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<td></td>
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<tr>
<td>4. Your normal work (both outside the home and housework)?</td>
<td></td>
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<tr>
<td>5. Your relations with other people?</td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>6. Your sleep?</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>7. Your enjoyment of life?</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>
### Section 5 – DASS21

Please read each statement and circle a number 0, 1, 2 or 3 which indicates how much the statement applied to you over the past week. There are no right or wrong answers. Do not spend too much time on any statement.

*The rating scale is as follows:*

- **0** Did not apply to me at all
- **1** Applied to me to some degree, or some of the time
- **2** Applied to me to a considerable degree, or a good part of the time
- **3** Applied to me very much, or most of the time

<table>
<thead>
<tr>
<th>_statement</th>
<th><strong>Not at all</strong></th>
<th><strong>Some of the time</strong></th>
<th><strong>A good part of the time</strong></th>
<th><strong>Most of the time</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I found it hard to wind down</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. I was aware of dryness of my mouth</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3. I couldn’t seem to experience any positive feeling at all</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. I experienced breathing difficulty (e.g. excessively rapid breathing, breathlessness in the absence of physical exertion)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5. I found it difficult to work up the initiative to do things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6. I tended to overreact to situations</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7. I experienced trembling (e.g. in the hands)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>8. I felt that I was using a lot of nervous energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>9. I was worried about situations in which I might panic and make a fool of myself</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>10. I felt that I had nothing to look forward to</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>11. I found myself getting agitated</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>12. I found it difficult to relax</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>13. I felt down-hearted and blue</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>14. I was intolerant of anything that kept me from getting on with what I was doing</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>15. I felt I was close to panic</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>16. I was unable to become enthusiastic about anything</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>17. I felt I wasn’t worth much as a person</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>18. I felt that I was rather touchy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>19. I was aware of the action of my heart in the absence of physical exertion (e.g. a sense of heart rate increase, heart missing a beat)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>20. I felt scared without any good reason</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>21. I felt that life was meaningless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
Section 6 – PSEQ

Rate how confident you are that you can do the following things at present despite the pain. Circle one of the numbers on the scale under each item, where 0 = Not at all confident and 6 = Completely confident.

Remember this questionnaire is not asking whether or not you have been doing these things, but rather how confident you are that you can do them at present, despite the pain.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I can enjoy things, despite the pain</td>
<td></td>
<td>Not at all confident</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>2. I can do most of the household chores (e.g. tidying up, washing dishes, etc.) despite the pain</td>
<td></td>
<td>Not at all confident</td>
<td></td>
<td></td>
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<tr>
<td>3. I can socialise with my friends or family members as often as I used to do, despite the pain</td>
<td></td>
<td>Not at all confident</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>4. I can cope with my pain in most situations</td>
<td></td>
<td>Not at all confident</td>
<td></td>
<td></td>
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<tr>
<td>5. I can do some form of work, despite the pain (includes housework, paid and unpaid work)</td>
<td></td>
<td>Not at all confident</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>6. I can still do many of the things I enjoy doing, such as hobbies or leisure activity, despite the pain</td>
<td></td>
<td>Not at all confident</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>7. I can cope with my pain without medication</td>
<td></td>
<td>Not at all confident</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>8. I can still accomplish most of my goals in life, despite the pain</td>
<td></td>
<td>Not at all confident</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>9. I can live a normal lifestyle, despite the pain</td>
<td></td>
<td>Not at all confident</td>
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<tr>
<td>10. I can gradually become more active, despite the pain</td>
<td></td>
<td>Not at all confident</td>
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</table>
Section 7 – PCS

Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures or surgery.

We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Using the scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>To a slight degree</th>
<th>To a moderate degree</th>
<th>To a great degree</th>
<th>All the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I worry all the time about whether the pain will end</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. I feel I can’t go on</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. It’s terrible and I think it’s never going to get any better</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. It’s awful and I feel it overwhelms me</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. I feel I can’t stand it anymore</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. I become afraid that the pain will get worse</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. I keep thinking of other painful events</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. I anxiously want the pain to go away</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9. I can’t seem to keep it out of my mind</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>10. I keep thinking about how much it hurts</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>11. I keep thinking about how badly I want the pain to stop</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>12. There’s nothing I can do to reduce the intensity of the pain</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>13. I wonder whether something serious may happen</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Thank you for completing this questionnaire
1. Please use the scale below to tell us how intense your pain is. Place an "X" through the number that best describes the intensity of your pain.

<table>
<thead>
<tr>
<th>No pain</th>
<th>1 2 3 4 5 6 7 8 9 10</th>
<th>The most intense pain sensation imaginable</th>
</tr>
</thead>
</table>

2. Please use the scale below to tell us how sharp your pain feels. Words used to describe "sharp" feelings include "like a knife," "like a spike," "jabbing" or "like jolts."

<table>
<thead>
<tr>
<th>Not sharp</th>
<th>1 2 3 4 5 6 7 8 9 10</th>
<th>The most sharp sensation imaginable (&quot;like a knife&quot;)</th>
</tr>
</thead>
</table>

3. Please use the scale below to tell us how hot your pain feels. Words used to describe very hot pain include "burning" and "on fire."

<table>
<thead>
<tr>
<th>Not hot</th>
<th>1 2 3 4 5 6 7 8 9 10</th>
<th>The most hot sensation imaginable (&quot;on fire&quot;)</th>
</tr>
</thead>
</table>

4. Please use the scale below to tell us how dull your pain feels. Words used to describe very dull pain include "like a dull toothache," "dull pain," "aching" and "like a bruise."

<table>
<thead>
<tr>
<th>Not dull</th>
<th>1 2 3 4 5 6 7 8 9 10</th>
<th>The most dull sensation imaginable</th>
</tr>
</thead>
</table>

5. Please use the scale below to tell us how cold your pain feels. Words used to describe very cold pain include "like ice" and "freezing."

<table>
<thead>
<tr>
<th>Not cold</th>
<th>1 2 3 4 5 6 7 8 9 10</th>
<th>The most cold sensation imaginable (&quot;freezing&quot;)</th>
</tr>
</thead>
</table>

6. Please use the scale below to tell us how sensitive your skin is to light touch or clothing. Words used to describe sensitive skin include "like sunburned skin" and "raw skin."

<table>
<thead>
<tr>
<th>Not sensitive</th>
<th>1 2 3 4 5 6 7 8 9 10</th>
<th>The most sensitive sensation imaginable (&quot;raw skin&quot;)</th>
</tr>
</thead>
</table>

7. Please use the scale below to tell us how itchy your pain feels. Words used to describe itchy pain include "like poison oak" and "like a mosquito bite."

<table>
<thead>
<tr>
<th>Not itchy</th>
<th>1 2 3 4 5 6 7 8 9 10</th>
<th>The most itchy sensation imaginable (&quot;like poison oak&quot;)</th>
</tr>
</thead>
</table>

8. Which of the following best describes the time quality of your pain? Please check only one answer.

- I feel a background pain all of the time and occasional flare-ups (break-through pain) some of the time.
  
  Describe the background pain:

- I feel a single type of pain all the time. Describe this pain:

- I feel a single type of pain only sometimes. Other times, I am pain free.
  
  Describe this occasional pain:

9. Now that you have told us the different physical aspects of your pain, the different types of sensations, we want you to tell us overall how unpleasant your pain is to you. Words used to describe very unpleasant pain include "miserable" and "intolerable. " Remember, pain can have a low intensity, but still feel extremely unpleasant, and some kinds of pain can have a high intensity but be very tolerable. With this scale, please tell us how unpleasant your pain feels.

<table>
<thead>
<tr>
<th>Not unpleasant</th>
<th>1 2 3 4 5 6 7 8 9 10</th>
<th>The most unpleasant sensation imaginable (&quot;intolerable&quot;)</th>
</tr>
</thead>
</table>

10. Lastly, we want you to give us an estimate of the severity of your deep versus surface pain. We want you to rate each location of pain separately. We realize that it can be difficult to make these estimates, and most likely it will be a "best guess," but please give us your best estimate.

**HOW INTENSE IS YOUR DEEP PAIN?**

<table>
<thead>
<tr>
<th>No deep pain</th>
<th>1 2 3 4 5 6 7 8 9 10</th>
<th>The most intense deep pain sensation imaginable</th>
</tr>
</thead>
</table>

**HOW INTENSE IS YOUR SURFACE PAIN?**

<table>
<thead>
<tr>
<th>No surface pain</th>
<th>1 2 3 4 5 6 7 8 9 10</th>
<th>The most intense surface pain sensation imaginable</th>
</tr>
</thead>
</table>
# SHORT-FORM McGill Pain Questionnaire

**PATIENT'S NAME:** __________________________ 
**DATE:** __________

<table>
<thead>
<tr>
<th>PAIN QUALITY</th>
<th>NONE</th>
<th>MILD</th>
<th>MODERATE</th>
<th>SEVERE</th>
</tr>
</thead>
<tbody>
<tr>
<td>THROBBING</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>SHOOTING</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>STABBING</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>SHARP</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>CRAMPING</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>GNAWING</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>HOT-BURNING</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>ACHING</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>HEAVY</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>TENDER</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>SPLITTING</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>TIRED-EXHAUSTING</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>SICKENING</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>FEARFUL</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>PUNISHING-CRUUEL</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

---

**NO PAIN**  | **WORST POSSIBLE PAIN**

0 NO PAIN
1 MILD
2 DISCOMFORTING
3 DISTRESSING
4 HORRIBLE
5 EXCRUCIATING

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Multiple Sclerosis Quality of Life

(MSQOL)-54 Instrument

For Further Information, Contact:

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C-128 RNRC; Box 951769
Los Angeles, CA 90095-1769
Voice: 310.206.7671
Fax: 310.794.7716
INSTRUCTIONS:

This survey asks about your health and daily activities. Answer every question by circling the appropriate number (1, 2, 3,...).

If you are unsure about how to answer a question, please give the best answer you can and write a comment or explanation in the margin.

Please feel free to ask someone to assist you if you need help reading or marking the form.

1. In general, would you say your health is:
   (circle one number)
   Excellent......................................1
   Very good.....................................2
   Good............................................3
   Fair.............................................4
   Poor............................................5

2. Compared to one year ago, how would you rate your health in general now?
   (circle one number)
   Much better now than one year ago...............1
   Somewhat better now than one year ago...........2
   About the same ...................................3
   Somewhat worse now than one year ago ..........4
   Much worse now than one year ago ............5
3-12. The following questions are about activities you might do during a typical day. Does *your health* limit you in these activities? If so, how much? (Circle 1, 2, or 3 on each line)

<table>
<thead>
<tr>
<th></th>
<th>Yes, Limited a Lot</th>
<th>Yes, Limited a Little</th>
<th>No, Not Limited at All</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5. Lifting or carrying groceries</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6. Climbing several flights of stairs</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7. Climbing one flight of stairs</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>8. Bending, kneeling, or stooping</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>9. Walking more than a mile</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>10. Walking several blocks</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>11. Walking one block</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>12. Bathing and dressing yourself</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
13-16. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

(Circle one number on each line)

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>13. Cut down on the <strong>amount of time</strong> you could spend on work or other activities</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>14. Accomplished <strong>less</strong> than you would like</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>15. Were limited in the <strong>kind</strong> of work or other activities</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>16. Had <strong>difficulty</strong> performing the work or other activities (for example, it took extra effort)</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

17-19. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious).

(Circle one number on each line)

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>17. Cut down on the <strong>amount of time</strong> you could spend on work or other activities</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>18. Accomplished <strong>less</strong> than you would like</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>19. Didn’t do work or other activities as <strong>carefully</strong> as usual</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
20. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?  

(circle one number)

Not at all...............................1  
Slightly .................................2  
Moderately .........................3  
Quite a bit ...............................4  
Extremely ...............................5  

**Pain**

21. How much **bodily** pain have you had during the **past 4 weeks**?

(circle one number)

None ................................. 1  
Very mild ...............................2  
Mild ....................................3  
Moderate ...............................4  
Severe ................................. 5  
Very severe ................................6  

22. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

(circle one number)

Not at all............................... 1  
A little bit ...............................2  
Moderately ...............................3  
Quite a bit ...............................4  
Extremely ...............................5
23-32. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks... (Circle one number on each line)

<table>
<thead>
<tr>
<th>Question</th>
<th>All of the Time</th>
<th>Most Of the Time</th>
<th>A Good Bit of the Time</th>
<th>Some of the Time</th>
<th>A Little of the Time</th>
<th>None of the Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>23. Did you feel full of pep?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>24. Have you been a very nervous person?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>25. Have you felt so down in the dumps that nothing could cheer you up?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>26. Have you felt calm and peaceful?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>27. Did you have a lot of energy?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>28. Have you felt downhearted and blue?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>29. Did you feel worn out?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>30. Have you been a happy person?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>31. Did you feel tired?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>32. Did you feel rested on waking in the morning?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>
33. During the **past 4 weeks**, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

(circle one number)

- All of the time .................. 1
- Most of the time .................. 2
- Some of the time .................. 3
- A little of the time ................. 4
- None of the time .................. 5

**Health in General**

34-37. How TRUE or FALSE is **each** of the following statements for you.

(Circle one number on each line)

<table>
<thead>
<tr>
<th></th>
<th>Definitely True</th>
<th>Mostly True</th>
<th>Not Sure</th>
<th>Mostly False</th>
<th>Definitely False</th>
</tr>
</thead>
<tbody>
<tr>
<td>34. I seem to get sick a little easier than other people</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>35. I am as healthy as anybody I know</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>36. I expect my health to get worse</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>37. My health is excellent</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
### Health Distress

How much of the time during the **past 4 weeks**...

(Circle one number on each line)

<table>
<thead>
<tr>
<th></th>
<th>All of the Time</th>
<th>Most of the Time</th>
<th>A Good Bit of the Time</th>
<th>Some of the Time</th>
<th>A Little of the Time</th>
<th>None of the Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>38. Were you discouraged by your health problems?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>39. Were you frustrated about your health?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>40. Was your health a worry in your life?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>41. Did you feel weighed down by your health problems?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>
### Cognitive Function

How much of the time during the **past 4 weeks**...

(Circle one number on each line)

<table>
<thead>
<tr>
<th>Question</th>
<th>All of the Time</th>
<th>Most of the Time</th>
<th>A Good Bit of the Time</th>
<th>Some of the Time</th>
<th>A Little of the Time</th>
<th>None of the Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>42. Have you had difficulty concentrating and thinking?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>43. Did you have trouble keeping your attention on an activity for long?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>44. Have you had trouble with your memory?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>45. Have others, such as family members or friends, noticed that you have trouble with your memory or problems with your concentration?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>
# Sexual Function

46-50. The next set of questions are about your sexual function and your satisfaction with your sexual function. Please answer as accurately as possible about your function during the last 4 weeks only.

How much of a problem was each of the following for you during the past 4 weeks?

<table>
<thead>
<tr>
<th>(Circle one number on each line)</th>
<th>Not a problem</th>
<th>A Little of a Problem</th>
<th>Somewhat of a Problem</th>
<th>Very Much a Problem</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MEN</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>46. Lack of sexual interest</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>47. Difficulty getting or keeping an erection</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>48. Difficulty having orgasm</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>49. Ability to satisfy sexual partner</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(Circle one number on each line)</th>
<th>Not a problem</th>
<th>A Little of a Problem</th>
<th>Somewhat of a Problem</th>
<th>Very Much a Problem</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WOMEN</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>46. Lack of sexual interest</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>47. Inadequate lubrication</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>48. Difficulty having orgasm</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>49. Ability to satisfy sexual partner</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
50. Overall, how satisfied were you with your sexual function during the past 4 weeks?

(circle one number)

Very satisfied.......................... 1
Somewhat satisfied...................... 2
Neither satisfied nor dissatisfied ........ 3
Somewhat dissatisfied............... 4
Very dissatisfied...................... 5

51. During the past 4 weeks, to what extent have problems with your bowel or bladder function interfered with your normal social activities with family, friends, neighbors, or groups?

(circle one number)

Not at all ................................. 1
Slightly.................................. 2
Moderately ............................... 3
Quite a bit ................................ 4
Extremely ................................ 5

52. During the past 4 weeks, how much did pain interfere with your enjoyment of life?

(circle one number)

Not at all ................................. 1
Slightly.................................. 2
Moderately ............................... 3
Quite a bit ................................ 4
Extremely ................................ 5
53. Overall, how would you rate your own quality-of-life?

Circle one number on the scale below:

[Scale from 10 to 0 with happy and sad faces]

Best Possible Quality-of-Life

Worst Possible Quality-of-Life
As bad as or worse than being dead

54. Which best describes how you feel about your life as a whole?

(circle one number)

Terrible ...................................... 1
Unhappy....................................... 2
Mostly dissatisfied ....................... 3
Mixed - about equally satisfied and dissatisfied ............... 4
Mostly satisfied........................... 5
Pleased ...................................... 6
Delighted .................................. 7
Appendix 3. Data Collection Sheets

Patient Questionnaire

<table>
<thead>
<tr>
<th>Study ID (not UR number)</th>
<th>Date:</th>
</tr>
</thead>
</table>

**Patient Details**

<table>
<thead>
<tr>
<th>Name</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Address</td>
<td></td>
</tr>
<tr>
<td>Contact Number</td>
<td></td>
</tr>
<tr>
<td>Date of Birth</td>
<td></td>
</tr>
</tbody>
</table>

**Pain-Related**

In the last 6 months

<table>
<thead>
<tr>
<th>Duration of pain</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of pain</td>
<td></td>
</tr>
<tr>
<td>(Superficial)</td>
<td></td>
</tr>
<tr>
<td>(Deep)</td>
<td></td>
</tr>
<tr>
<td>(Superficial and Deep)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Temporal aspects of pain</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(Onset before other symptoms)</td>
<td></td>
</tr>
<tr>
<td>(Onset same year as other symptoms)</td>
<td></td>
</tr>
<tr>
<td>(Onset 1-5 years before other symptoms)</td>
<td></td>
</tr>
<tr>
<td>(Onset 6-10 years after other symptoms)</td>
<td></td>
</tr>
<tr>
<td>(Onset 10 years after other symptoms)</td>
<td></td>
</tr>
</tbody>
</table>

**Site of pain**

![ Tuple of human figures showing pain sites on both sides of the body. ]

Right: Left. Left: Right.
### Pain Treatments and Access

**In the last 6 months**

<table>
<thead>
<tr>
<th>Medication Use (Current)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(Non-opioids, Opioids, Anti-inflammatory, Muscle relaxants and Anticonvulsants, Antidepressants and Anxiolytics)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medication Use (Previous 6 months)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(Non-opioids, Opioids, Anti-inflammatory, Muscle relaxants and Anticonvulsants, Antidepressants and Anxiolytics)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Manipulation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(Physical/electrical, Change in temperature, Support, Exercise, Rest or Sleep, Psychosocial)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Miscellaneous</td>
<td></td>
</tr>
<tr>
<td>(Breathing, Reduce stress, relaxation, pain clinic, biofeedback, talk to people, put others first, not dwell on pain, deal with it, pray, meditation)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alternative</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(Acupuncture, chiropractor, Vitamins, Diet)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distraction</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(Keep Busy, Read, Handwork, Computer, Music)</td>
<td></td>
</tr>
</tbody>
</table>

### Perceived Barriers to Healthcare

**In the last 6 months**

<table>
<thead>
<tr>
<th>Environmental Barriers</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(Lack of transportation, Lack of finances, Lack of accessible pain or MS specialists, Lack of ramp/lift/steps)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cognitive or Communication</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(Inability to explain due to memory or speech difficulty)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other Difficulties</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(Side effects from medications, Fear of taking medication/dependence, Worry that</td>
<td></td>
</tr>
<tr>
<td>Pain not perceived as real, Nothing works so will not mention</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Number of visits to Healthcare in the last 12 months</td>
<td></td>
</tr>
<tr>
<td>Practitioners (General Practitioner, Neurologist, Rheumatologist, Rehabilitation physician, Pain specialist, Orthopaedic surgeon)</td>
<td></td>
</tr>
<tr>
<td>Allied Health (Physiotherapist, Occupational therapist, Orthotist, Podiatrist, Chiropractor, Acupuncturist, Hydrotherapist, Pharmacist)</td>
<td></td>
</tr>
<tr>
<td>Alternative (Masseur, Naturopath, Osteopath)</td>
<td></td>
</tr>
<tr>
<td>Do you experience any of the following symptoms or side-effects?</td>
<td>Enter a value (1-4) in the space below (1, absent; 2, mild; 3, moderate; 4, severe)</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Headache</td>
<td></td>
</tr>
<tr>
<td>Neck pain</td>
<td></td>
</tr>
<tr>
<td>Scalp pain</td>
<td></td>
</tr>
<tr>
<td>Tingling</td>
<td></td>
</tr>
<tr>
<td>Itching</td>
<td></td>
</tr>
<tr>
<td>Burning sensation</td>
<td></td>
</tr>
<tr>
<td>Skin redness</td>
<td></td>
</tr>
<tr>
<td>Sleepiness</td>
<td></td>
</tr>
<tr>
<td>Trouble concentrating</td>
<td></td>
</tr>
<tr>
<td>Acute mood change</td>
<td></td>
</tr>
<tr>
<td>Others (specify)</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 3. Cochrane Search Strategies

PsycINFO

S1 TX multiple sclerosis
S2 DE "Multiple Sclerosis"
S2 TX demyelinating disease
S4 DE "Demyelination"
S5 TX transverse myelitis
S6 DE "Myelitis"
S7 TX neurophilalitis optica
S8 TX optic neuritis
S9 TX encephalomyelitis acute disseminated
S10 DE "Encephalopathies"
S11 TX devic
S12 $1 or $2 or $3 or $4 or $5 or $6 or $7 or $8 or $9 or $10 or $11
S13 DE "Somatosensory Disorders"
S14 DE "Pain" OR DE "Aphasia" 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 dysesthesia or TX dysesthetenic
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 nociceptor* or musculoskeletal or chronic or intens* or threshold* or shoulder* or abdomin* or back or neuropath*)
S25 Ti pain N5 (refer* or refractory or intractable or receptor* or nociceptor* or musculoskeletal or chronic or intens* or threshold* or shoulder* or abdomin* or back or neuropath*)
S26 (Ti nociceptor* N5 neuron* OR Ti pain*)
S27 S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26
S23 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 therapy OR TX stretching OR TX tai chi OR TX yoga


S35 TX cognitive behavioral 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 hydrotherapy 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 aromatherapy 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 DRZ

S49 DE “Osteopathic Medicine”

S50 TX orthotics OR TX orthosis OR TX brace

S51 TX nonpharmaco OR TX non-pharmaco
AMED

S1 TX multiple sclerosis
S2 (DE "MULTIPLE SCLEROSIS")
S3 TX demyelinating disease*
S4 TX transverse myelitis
S5 TX neuritis optica
S6 TX optic neuritis
S7 TX encephalomyelitis acute disseminated
S8 (DE "ENCEPHALOMYELITIS")
S9 TX deoic
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 dysesthesia or TX dysesthetic
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 nociceptor* or musculoskeletal or chronic or intense* or threshold* or shoulder* or abdominal* or back or neuropath*)
S22 TI pain N5 (refer* or refractory or intractable or receptor* or nociceptor* or musculoskeletal or chronic or intense* or threshold* or shoulder* or abdominal* or back or neuropath*)
S23 (TI nociceptor* N5 neuron* OR TI pain*
S24 S17 or S18 or S19 or S20 or S21 or S22 or S23
S25 S10 and S16 and S29
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. demyel.sh
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
19. 14 or 15 or 18 or 17 or 18
20. pain, intractable.sh
21. pain measurement.sh
22. pain threshold.sh
23. nociceptors.sh
24. [pain adj5 (refractory OR refractory OR intractable OR receptor* OR nocicept* OR musculoskeletal OR chronic OR intensity 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 25 or 24 or 25
27. 13 or 18 or 28
Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:
Young, Jamie

Title:
Non-pharmacological management of chronic pain in multiple sclerosis and rehabilitation outcomes

Date:
2019

Persistent Link:
http://hdl.handle.net/11343/230658

File Description:
Final thesis file

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