Title: Physiotherapy rehabilitation for people with progressive Multiple Sclerosis: a systematic review.

Authors: Evan Campbell, MRes[a], Elaine H. Coulter, PhD[a], Paul G. Mattison, M.D[b], Linda Miller, MPhil[b,c], Angus McFadyen, PhD[d], Lorna Paul, PhD[a]

Affiliations: [a]School of Medicine, The University of Glasgow; [b]MS Service, NHS Ayrshire and Arran; [c]School of Health and Life Sciences, Glasgow Caledonian University; [d]AKM-Stats, Statistical Consultant, Glasgow.

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Corresponding Author: Evan Campbell, School of Medicine, The University of Glasgow, 59 Oakfield Avenue, Glasgow, G12 8LL, 0141 330 7154, e.campbell.4@research.gla.ac.uk

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Abstract

Objective: To assess the efficacy of physiotherapy interventions, including exercise therapy, for the rehabilitation of people with progressive Multiple Sclerosis.

Data Sources: Five databases (Cochrane Library, Physiotherapy Evidence Database (PEDro), Web of Science Core Collections, Medline, EMBASE) and reference lists of relevant articles were searched.

Study Selection: Randomised experimental trials which included participants with progressive multiple sclerosis and investigated a physiotherapy intervention or an intervention containing a physiotherapy element were included.

Data Extraction: Data were independently extracted using a standardised form and methodological quality was assessed using the PEDro scale.

Data Synthesis: Thirteen studies (described by 15 articles) were identified; scoring between 5 and 9 out of 10 on the PEDro scale. Eight interventions were assessed: exercise therapy, multi-disciplinary rehabilitation, functional electrical stimulation, botulinum toxin type A injections and manual stretches, inspiratory muscle training, therapeutic standing, acupuncture and body weight supported treadmill training. All studies, apart from one, produced positive results in at least one outcome measure, however, only one article used a power calculation to determine their sample size and due to 'drop outs' the results were subsequently underpowered.

Conclusions: This review suggests that physiotherapy may be effective for the rehabilitation of people with progressive Multiple Sclerosis. However, further appropriately powered studies are required.

Keywords: Multiple Sclerosis, physical therapy modalities, exercise, rehabilitation, review

List of abbreviations

BTX-A	botulinum toxin type A
BWSTT	body weight supported treadmill training
EDSS	expanded disability status scale
FES	functional electrical stimulation
MCID	minimal clinically important difference
MeSH	medical subject headings
MS	multiple sclerosis
PEDro	Physiotherapy Evidence Database
PPMS	primary progressive multiple sclerosis
RRMS	relapsing remitting multiple sclerosis
SPMS	secondary progressive multiple sclerosis

Multiple Sclerosis (MS) is a chronic inflammatory autoimmune demyelinating disease of the central nervous system resulting in grey matter and axonal loss.[1, 2] Currently, there are an estimated 130,000 cases of MS in the UK with an incidence of 11.52 per 100,000 women and 4.84 per 100,000 men.[3] Approximately 15% of all individuals with MS are diagnosed with Primary Progressive MS (PPMS) and 80% of those diagnosed with Relapsing Remitting MS (RRMS) go on to develop Secondary Progressive MS (SPMS).[4] There is a strong evidence base for interventions for the treatment of people with RRMS but whilst studies are currently ongoing there are limited effective treatments for people with progressive MS.[5] The Progressive MS Alliance have highlighted this area as a priority, especially for those with a higher level of disability.[5]

There is a growing body of literature investigating the benefits of physiotherapy (a physical intervention that may be used by a physiotherapist, including physical activity and exercise interventions) in the rehabilitation of people with MS. In a series of review papers, exercise therapy and physical activity have been shown to be generally beneficial to those with MS who are not suffering a relapse,[6-8] as well as having positive effects on fatigue,[9, 10] health related quality of life[11] and muscle strength[12] in those with a mild to moderate disability. Physiotherapy has also been shown to have a positive effect on balance and mobility.[13-15] However, when the level of disability increases efficacy of physiotherapy is less compelling.[13, 15] Whilst some studies have considered their results in terms of disability levels, none have made a distinction between RRMS and progressive MS. To date, there has not been a published review examining the evidence for physiotherapy for the rehabilitation of people with progressive MS. Consequently, the aim of this systematic review is to assess the efficacy of physiotherapy rehabilitation for people with progressive MS.

Methods

In December 2014 a search was conducted of the following electronic databases: the Cochrane Library, Physiotherapy Evidence Database (PEDro), Web of Science Core Collections, Medline and Embase. No restrictions were placed on publication date and studies were limited to English language only. Individual search strategies were made up of keywords and Medical Subject Headings (MeSH) headings (Table 1). Reference lists of relevant articles were also searched.

To be included in the review, articles had to; be published in English, include solely participants with progressive forms of MS or where there was a combination of types of MS distinct results for the different types of MS are presented, evaluate a physiotherapy intervention(s) or an intervention containing a physiotherapy element, have randomised participants, have a comparison group and use at least one objective outcome measure. Articles were excluded if they were non-human studies, conference abstracts or posters. Articles were initially screened by title and abstract. Full articles were then read. When there was ambiguity in meeting the inclusion criteria the authors were contacted for clarification.

Quality assessment (external validity, internal validity and the reporting of statistics) was assessed using the PEDro scale which has been shown to be reliable and valid in rating methodological quality of studies.[16, 17] The 11 point scale was given a score out of ten (no point was awarded for the initial item of stating inclusion and exclusion criteria) as per the

guidelines. Scoring was carried out by three reviewers (EC, LP and EHC). A pilot quality assessment was conducted to ensure consistency where all three reviewers read and independently scored one paper, following which, scoring was discussed and agreed. Each article was then scored independently by two reviewers and scores compared. When there was a discrepancy in score, differences were agreed via discussion which included the third reviewer. Quality assessment was entirely based on the content of the study in the published article. When two articles were from the same study but reported different outcome measures they were combined and considered as a single study. Data extraction was done independently using a standardised form into evidence tables. The following data were extracted: study design, sample size, drop-out rate, type of MS of participants, Expanded Disability Status Scale (EDSS) range,[18] intervention type, length, frequency, setting, time points of measurement, control intervention, outcome measures, baseline measurements and main findings.

Results

Outcome of search

From the electronic search 1027 articles were identified and four articles were identified from relevant article's reference lists (Figure 1). Of these, 197 were duplicates leaving 834 unique publications for screening by title and abstract. After screening 783 articles were excluded. Full texts of 51 articles were read and 36 were excluded. From the remaining 15

articles; there were two instances of two papers that were from the same study but had used different outcome measures and so they were combined.[19-22] Thus 13 studies (published within 15 articles) were included within this review (Figure 1).

Quality assessment, study design and sample characteristics

PEDro scores ranged from 5-9 out of 10 (Table 2). Lower scores were mainly due to lack of blinding of patients, therapists or assessors and not conducting analyses with intention to treat when appropriate. Only one article[19] supplied a power calculation used to determine their sample size but due to 'drop outs' the results were subsequently underpowered. From the remaining studies, six highlighted their lack of power calculation[23-28] and four highlighted their small sample size[29-32] as methodological limitations; two studies did not mention either a power calculation or comment on their sample size.[21, 22, 33]

From the studies included in the review there were nine randomised controlled trials (described in 11 articles),[19-22, 24, 25, 27, 29-31, 33] two randomised trials[26, 28] and two randomised crossover trials.[23, 32] The length of intervention ranged from 15 days to 24 weeks and the frequency of intervention ranged from twice weekly to daily. Eight studies did not follow up participants after the intervention period[19-24, 27-29, 32, 33] and four studies included a follow up assessment at 4,[31] 8,[25] 10[30] and 18 weeks[26] after the intervention had ended (Table 3).

Six studies investigated physiotherapy as part of a multi-dimensional intervention[21, 22, 26-28, 30, 33] and seven studies investigated the use of only a physiotherapy intervention.[19, 20, 23-25, 29, 31, 32] Study sample sizes ranged from 6-111 participants, EDSS scores ranged from 1.5-9.5. Eight studies included participants with both SPMS and PPMS[21-24, 27, 31-33] and five studies included only participants with SPMS.[19, 26, 28-30] There were no studies that included only participants with PPMS (Table 3). There were 45 outcome measures used across the 15 articles with few instances of commonality despite often measuring the same symptom or functional status. Baseline measurements of all outcome measures and final values or change values for the main findings of each study can be found in supplementary Table S1.

Interventions

There were four instances when the same type of intervention was implemented: physiotherapy as part of a multi-disciplinary rehabilitation intervention was investigated by two studies,[21, 22, 33] Functional Electrical Stimulation (FES) was investigated by two studies,[19, 20, 28] exercise therapy was investigated by three studies,[24, 25, 27] and a combination of botulinum toxin type A (BTX-A) injections and manual stretches was investigated by two studies.[26, 30] The following interventions were investigated by one study each: acupuncture[29]; inspiratory muscle training[31]; Body Weight Supported Treadmill Training (BWSTT) and robotic orthotics[32] and therapeutic standing using a standing frame.[23]

Physiotherapy as part of a multi-disciplinary rehabilitation programme

The evidence is positive regarding the efficacy of a six week multi-disciplinary rehabilitation programme for the rehabilitation of people with progressive MS. The two studies (described in three articles) which used multi-disciplinary rehabilitation programmes found improvements in disability when measured using the Functional Independence Measure, however the EDSS level remained unchanged.[21, 22, 33] Improvements were also found in depression, social experience, quality of life and fatigue and these were maintained at six weeks post intervention[21, 22] (Table 3). The multi-disciplinary rehabilitation programmes differed both in delivery setting and the control group interventions, however both had positive effects.

Functional Electrical Stimulation

The evidence is conflicting regarding the efficacy of using FES as an intervention for the rehabilitation of people with progressive MS. The two studies which used FES (described in three articles) found positive results for an orthotic effect and decrease in falls with FES in comparison to a home exercise plan aimed at improving core stability.[19, 20, 28] However, Taylor et al. found their FES intervention produced a therapeutic effect in gait quality, while Barret et al. found only their home exercise plan produced a therapeutic effect on walking speed and endurance. These conflicting results may be due to differences in duration of the interventions, the control group interventions and the use of gluteal stimulation in addition to peroneal FES by Taylor et al. (Table 3).

Exercise therapy

The evidence is inconclusive regarding the efficacy of using exercise therapy for the rehabilitation of people with progressive MS. Two of the three studies which used exercise therapy investigated endurance training in a clinical environment[24, 27] and the third investigated resistance training and functional exercises in a home environment.[25] The two endurance studies measured fitness and found improvements but only Briken et al. reported a significant improvement.[24, 27] Briken et al. also reported significant improvements in mobility, depression, fatigue and cognitive function and Miller et al. reported significant improvements in muscle strength and anxiety. There was no significant improvement in any of the other outcomes of these studies (Table 3). Differences in results between these studies may be due to differences in inclusion criteria and the intervention protocol. Skjerbaek et al. and Miller et al. included participants with a higher level of disability (EDSS 6.5-8.0) while Briken et al. included participants with a moderate disability (EDSS 4-6). Skjerbaek et al. and Briken et al. conducted their final assessments at four and six weeks respectively without a follow up assessment while Miller et al. did a follow up assessment eight weeks after their eight week intervention (Table 3).

Botulinum toxin type A injections and manual stretches

The evidence in this review is positive regarding the efficacy of using a combination of BTX-A injections and manual stretches for the rehabilitation of people with progressive MS. However, it is unclear which combination is the most effective. The two studies which used BTX-A injections and manual stretches differed as Giovanelli et al.[30] compared BTX-A injections to BTX-A injections and manual stretches whilst Paolini et al.[26] conducted a three arm randomised trial investigating different combinations of BTX-A injections, manual stretches and segmental muscle vibration (Table 3). Each group experienced improvements in spasticity, with those who only received BTX-A injections experiencing the least improvement.[30] Significant improvements were also found in subjective relief of symptoms,[30] fatigue and activities of daily living[26] in those who received a combination of BTX-A injections and manual stretches, however improvements in spasticity were not maintained at 18 weeks post intervention compared to six weeks post intervention.[26] In contrast, interventions incorporating segmental muscle vibration also produced significant improvements in spasticity however these improvements were maintained at follow up assessments[26] (Table 3).

Acupuncture

The evidence is inconclusive regarding the efficacy of acupuncture for the rehabilitation of people with progressive MS. There was only one study that investigated Chinese Medical acupuncture in comparison to minimal acupuncture[29] (a form of sham acupuncture where needles are inserted to a shallower depth and not at true acupuncture points[34]). Minimal

acupuncture produced significant improvements in the psychological sub-score of the Multiple Sclerosis Impact Scale compared to Chinese Medical acupuncture. No changes were seen in any other outcomes (Table 3).

Inspiratory muscle training

The evidence in this review is positive regarding the efficacy of using inspiratory muscle training for the rehabilitation of people with progressive MS, although only one study was found which investigated this technique. The study investigated the use of an inspiratory muscle trainer in comparison to deep breathing exercises.[31] A significant improvement was found in maximal inspiratory pressure and maximal expiratory pressure in those using the inspiratory muscle trainer. No changes were seen in any other outcomes (Table 3).

Body Weight Supported Treadmill Training and robotic orthotics

The evidence in this review is inconclusive regarding the efficacy of BWSTT and robotic orthotics for the rehabilitation of people with progressive MS. Only one study investigated BWSTT compared to BWSTT and robotic orthotics in a randomised crossover trial.[32] There was a trend towards improvement in double-limb support time in those receiving BWSTT compared to those receiving BWSTT and robotic orthotics. At the end of the study, all participants showed significant improvements in walking speed, endurance, double limb

support time and disability but not in step length ratio (Table 3). However, after the washout period, values had not returned to baseline. Therefore between group analyses were performed after the initial three week intervention period.

Therapeutic standing

Similar to other physiotherapeutic interventions only one study investigated the efficacy of therapeutic standing for the rehabilitation of people with progressive MS. The use of a standing frame was compared to a daily home exercise programme consisting of abdominal crunches, hip rolls, lumbar rolls and bridging.[23] Therapeutic standing produced significant improvements in passive hip and ankle range of motion and a trend towards improvement in ankle spasticity; while the home exercise programme resulted in trends towards improvement in frequency of leg spasms (Table 3).

Overall outcome of studies

Generally the articles presented a positive effect of physiotherapy for the rehabilitation of people with progressive MS. Thirteen studies (described in 15 articles) found that the intervention group improved more than the comparison or control group in at least one outcome measure.[19-25, 27, 30, 31, 33] One study only found statistically significant improvements in within group analysis,[26] one study reported that neither group made an improvement

large enough for statistical significance[27] and one study found that participants who received the control treatment improved more than those who received the intervention.[29] It is important to note that only one study used a power calculation to determine the required sample size however due to 'drop outs' the results were subsequently underpowered.

Clinical significance of improvements

From the papers included in this review, where a statistically significant change in the outcome measure was reported data detailing minimal clinically important differences (MCID) in people with MS was sought. Only four outcome measures had MCID data available; the timed 25 foot walk test (improvement of 17.2%),[35] the six minute walk test (improvement of 21.6 m),[36] the fatigue impact scale (improvement of 10-20 points)[37] and the physical sub-score of the multiple sclerosis impact scale (improvement of 8 points).[38] Four studies had statistically significant results that used at least one of these outcome measures (Table 4).[22, 24, 28, 32] All of these results were above the level of MCID for people with MS indicating a positive perspective for using physiotherapy in the rehabilitation of people with progressive MS. The four trials used four different interventions; multidisciplinary rehabilitation,[22] FES,[28] exercise therapy[24] and BWSTT and robotic orthotics.[32] Three trials included participants who were moderately affected by MS (EDSS levels 4-6.5)[24, 28, 32] and one had a wider range and included those more severely affected (EDSS levels 4-8)[22] (Table 4). Two of the studies used the fatigue impact scale,[22, 24] both

produced similar levels of change despite Patti et al.[22] including participants with a wider EDSS range and higher levels of fatigue at baseline. Similarly, two studies used the six minute walk test,[24, 32] both produced similar improvements despite differences in distance walked at baseline.

Discussion

Overall the evidence presented in this review is positive regarding the efficacy of physiotherapy for the rehabilitation of people with progressive MS although it should be noted that the evidence is generally weak due to the variation in interventions and a lack of power within studies.

The Progressive MS Alliance, and previous reviews, have highlighted that research regarding progressive MS and higher levels of disability is an area requiring further work.[5, 13, 15] Only four studies within the review included participants with a high level of disability (EDSS $\geq$ 6.5) (n=62), five studies did not make a distinction in the level of disability of their participants (n=242) and four studies included only participants with a mild to moderate level of disability (EDSS $\leq$ 6.0) (n=178). Exercise therapy was the only intervention where the effects were compared across disability levels.[25, 26, 30] The results of these studies agreed with those of previously published reviews which found exercise therapy produced improvements in fatigue in those with a mild to moderate disability,[9] while no significant results were found in those with a higher level of disability.[6]

The results of this review were consistent with those found in systematic reviews of the other interventions for either MS or similar patient groups. Previously published reviews investigating the efficacy of physiotherapy interventions for people with MS found that multi-disciplinary rehabilitation programmes increased participation (as a result of a decrease in disability) and quality of life[39]; were unable to draw a conclusion as to the effectiveness of acupuncture[40]; found respiratory muscle trainers increased maximal inspiratory and expiratory pressure[41] and that BWSTT and BWSTT with robotic orthotics both improved walking speed, double-limb support time, endurance and step length ratio.[42] However there was no improvement in step length ratio in the study presented in this review. Two reviews assessing the efficacy of FES in chronic stroke found it had a good orthotic effect[43] but were unable to conclude on the efficacy of a therapeutic effect.[44] Reviews assessing interventions for neurological impairments were unable to ascertain the most effective adjunct therapy to BTX-A injections in the treatment of spasticity[45] and that therapeutic standing produced improvements in ankle range of motion.[46] However, the similarity between the results of this review and other reviews for the same interventions in similar patient groups such as RRMS should be approached with caution due to the previously mentioned methodological weaknesses in the body of evidence presented.

Symptom management and rehabilitation is one of the five key research priorities identified by the Progressive MS Alliance.[5] However, impact on quality of life and participation should also be a consideration. Thus, identifying the patient groups who would experience the greatest improvement in clinical outcomes to particular interventions, with the greatest impact upon quality of life and participation, would help establish the full effectiveness of interventions.

Study limitations

This review was limited to only include articles in published in English. It was further limited by the broad spectrum of physiotherapy as a discipline which led to variation in duration, dose, intensity and the type of interventions included.

Future Work

We recommend future work should be carried out to investigate physiotherapy interventions for people with progressive MS using adequately powered randomised trials with an appropriate control, long term follow up and adequate reporting.[47] Studies should, where possible, aim to use a core set of outcome measures[48] and use outcome measures for which there is available data of MCID for people with MS. Future research should also consider participants with PPMS and SPMS separately to investigate whether this has an effect on clinical outcomes. We also recommend investigation to ascertain which patient groups would experience largest improvements in quality of life from improvements in clinical outcomes.

Conclusion

In conclusion, the evidence within this review demonstrates that physiotherapy may be effective in the rehabilitation of people with progressive MS. This review which focussed on people with progressive MS had similar findings to reviews in similar patient groups. Further investigation, with appropriately powered studies and consistency in outcome measures between studies is required to strengthen this evidence base and conduct meta-analyses of the evidence.

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Table 1. Search strategies for electronic databases.

Database	Search Strategy
Cochrane library	(Progressive near/2 ("multiple sclerosis" or MS)) AND ((MeSH descriptor: [Physical Therapy Modalities] explode all trees) OR(MeSH descriptor: [Rehabilitation] explode all trees) OR (MeSH descriptor: [Exercise] explode all trees) OR (MeSH descriptor: [Resistance Training] explode all trees) OR (MeSH descriptor: [Transcutaneous Electric Nerve Stimulation] explode all trees) OR (MeSH descriptor: [Electric Stimulation] explode all trees) OR(MeSH descriptor: [Acupuncture] explode all trees))
Web of Science Core Collections	((progressive NEAR/2 (MS OR "Multiple Sclerosis")) AND ((physiotherap* OR "physical therapy") OR (rehabilit*) OR (exercise OR training) OR ("electrical stimulation" OR FES OR NMES OR TENS OR "neuromuscular stimulation") OR (acupuncture)
Embase via Ovid	((progressive adj2 ("multiple sclerosis" or MS)).mp.) AND ((home physiotherapy OR physiotherapy) OR (prevention OR rehabilitation OR therapy OR rehabilit*.mp. OR rehabilitation center OR rehabilitation care OR breathing exercise OR muscle exercise OR arm exercise OR treadmill exercise OR aerobic exercise OR static exercise OR leg exercise OR isokinetic exercise OR closed kinetic chain exercise OR open kinetic chain exercise OR exercise.mp. OR exercise tolerance OR isometric exercise OR isotonic exercise OR aquatic exercise OR dynamic exercise OR stretching exercise OR anaerobic exercise OR exercise OR nerve stimulation OR electrostimulation therapy OR electroacupuncture OR functional electrical stimulation OR neuromuscular electrical stimulation OR transcutaneous nerve stimulation OR acupuncture OR acup.mp. electrostimulation OR functional electrical stimulation OR muscle OR gait)
MEDLINE via OVID	((progressive adj2 ("multiple sclerosis" or MS)).mp.) AND (exp Exercise Therapy physiotherapy.mp. OR physical therapy.mp. OR rehabilitation OR "activities of daily living" OR exercise therapy OR motion therapy, continuous passive OR muscle stretching exercises OR plyometric exercise OR resistance training OR rehabilitation, vocational OR exp Exercise Therapy OR exp Plyometric Exercise OR exercise.mp. OR exp Exercise Movement Techniques OR exp Exercise OR Electric Stimulation OR electric stimulation therapy OR electroacupuncture OR spinal cord stimulation OR transcutaneous electric nerve stimulation OR Transcutaneous Electric Nerve Stimulation OR exp Acupuncture Therapy OR exp Acupuncture Analgesia OR exp Acupuncture OR acupuncture.mp.)
Pedro	“progressive AND multiple AND sclerosis”

Table 2. PEDro scores for included studies.

Author	Eligibility Criteria*	Random allocation	Concealed allocation	Baseline comparability	Participant blinding	Therapist blinding	Assessor blinding	<15% dropout	Intention -to-treat	Between-group difference	Point Estimate and Variability	Total (0-10)
Freeman et al.[33]	Y	Y	Y	Y	N	N	N	Y	N	Y	Y	6
Patti et al.[21]†	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Patti et al.[22]†	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Klefbeck and Hamrah Nedjad[31]	Y	Y	N	Y	N	N	N	Y	N	Y	Y	5
Baker et al.[23]	Y	Y	N	N	N	N	Y	Y	Y	Y	Y	6
Giovanelli et al.[30]‡	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	7
Donnellan & Shanley[29]	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9
Lo & Triche[32]	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	6
Barrett et al.[19]§	Y	Y	Y	Y	N	N	N	N	N	Y	Y	5
Esnouf et al.[20]§	Y	Y	Y	Y	N	N	Y	N	N	Y	Y	6
Miller et al.[25]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Paoloni et al.[26]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Taylor et al.[28]	Y	Y	Y	Y	N	N	Y	N	N	Y	Y	6
Briken et al.[24]	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
Skjerbaek et al.[27]	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	7

EC assessed all articles,[19-33] LP assessed 8 articles[19, 20, 23-26, 32, 33] and EHC assessed 8 articles.[21, 22, 26-31]

*No point awarded for stating eligibility criteria.

†Patti et al. 2002 and Patti et al. 2003 described the same study.

‡All three reviewers rated this paper initially and discussed results to ensure consistency.

§ Barrett et al. 2009 and Esnouf et al. 2010 described the same study.

Table 3. Evidence table

Author, date and design	**Sample size** **PPMS** **SPMS** **EDSS range** **Drop outs**	**Intervention, duration, length of session, frequency**	**Comparison/ control**	**Time Points (weeks)**	**Outcome measures***	**Main findings***
Freeman et al.[33] 1997 *RCT*	n=66 PPMS (n=6) SPMS (n=60) EDSS 5.0-9.5 Drop out: 4 (6%)	6 weeks, MDT in-patient rehabilitation, 45 min, 2/week (n=32)	Wait list control (n=34)	0, 6	Pri: EDSS, FIM, LHS	Between group: FIM (p<0.001), LHS (p<0.01)
Patti et al.[22] 2002 *RCT*	n= 111 PPMS (n=23) SPMS (n=88) EDSS 4-8 Drop out: 13 (12%)	12 weeks: 6 week MDT out-patient rehabilitation, 50-60 min, 6/week, followed by 6 week HEP, 60 min, 5/week (n=58)	HEP for 12 weeks (n=33)	0, 6, 12	Pri: EDSS, SF-36 Sec: BDI, SET, FIS	Between group: SF-36: RE subscale (p<0.005) all other subscales (p<0.001), BDI(p<0.001), SET (p<0.001), FIS (p<0.001)
Patti et al.[21] 2003 *RCT*	As above	As above	As above	As above	Pri: FIM Sec: EDSS	Between group: FIM (p<0.001)
Klefbeck and Hamrah Nedjad[31] 2003 *RCT*	n=15 progressive MS EDSS 6.5-9.5 Drop out: 1 (7%)	10 weeks: Inspiratory muscle trainer, 3 sets of 10 repetitions, twice every second day (n=7)	Normal treatment which had deep breath exercises, regular phone calls (n=8)	0, 10, 14	Pri: VC, FVC, FVC%, FEV FEV%, Max insp pressure, Max exp pressure, FSS, Borg scale	Between group: Max insp pressure (p<0.01) Within group: I: max exp pressure (p<0.02)
Baker et al.[23] 2007 *Randomised crossover design*	n= 6 progressive MS EDSS $\geq$ 7 Drop out: 0 (0%)	3 weeks: Standing frame,30 min/day (n=3) I+C swapped after 3 weeks (no washout period)	HEP of abdominal crunches, bridging, pelvic and lumbar rolls, 5 repetitions of 8 exercises (n=3)	0, 3, 6	Pri: Ashworth Scale, Spasm frequency, Resting ROM in supine	Between group: Resting ROM in supine: L ankle (p=0.020), R ankle (p=0.026), L hip (p=0.039), R hip (p=0.020) Within group: I: Ashworth scale, R ankle (p=0.08), L ankle (p=0.08) C: spasm frequency, R leg (p=0.06)
Giovanelli et al.[30] 2007	n=38 All SPMS	15 days: I: BTX-A injection in either upper limb (FDS, FCU,	BTX-A injection only (n=28)	0, 2, 4, 12	Pri: MAS, VAS of relief from spasticity in	Between group: MAS (p<0.01), VAS (p<0.01)

RCT	EDSS 3-7.5 Drop out: 2 (5%)	FCR) or lower limb (tibialis posterior, gastrocnemius, soleus) followed by 40min/day of passive movements to prevent muscle contractures (n=20)			injected muscle	
Donnellan & Shanley[29] 2008 *RCT*	n=14 All SPMS EDSS 1.5-7.0 Drop out: 1 (7%)	5 weeks: Chinese medical acupuncture (n=7)	Minimal acupuncture† , 5 weeks, twice a week (n=7)	0, 5	Pri: MSIS-29 phys, MSIS-29 psych Sec: FSS, GHQ-12	Between group (C vs I): MSIS-29 psych sub-score I (p=0.04)
Lo & Triche[32] 2008 *Randomised crossover design*	n=13 PPMS (n=5) SPMS (n=8) EDSS 4.9 SD 1.2 Drop out: 0 (0%)	12 weeks: BWSTT, 3 weeks, 2/week, 40 min, followed by 6 week washout then BWSTT and robot orthotics a/a (n=6) ‡	Same as I but BWSTT and robot orthotics first (n=7)	0, 3, 9, 12	Pri: EDSS, Timed 25 foot walk, 6 min walk, DST Sec: step length ratio	Between group: DST: (p=0.06) Within group: Whole sample: timed 25 foot walk (p=0.0002), 6 min walk (p=0.002), DST (p=0.0007) and EDSS (p=0.001)
Barrett et al.[19] 2009 *RCT*	n=53 All SPMS EDSS 4-6.5 Drop out: 7 (13%)	18 weeks, Peroneal FES, worn in daily life (n=20)	HEP of trunk and pelvic stability and lower limb strength, balance and control exercises, 18 weeks, 1-2/ day, 30 min (n=24)	0, 6, 12, 18	Pri: 10 m walk speed Sec: 3min walk distance	Within group: I with FES vs I without: 10 m walk speed (p=0.001), 3 min walk distance (p=0.004) C: 10 m walk speed (p=0.001) C: 3 min walk distance (p=0.005)
Esnouf et al.[20] 2010 *RCT*	n= 64 All SPMS EDSS 4-6.5 Drop out: 11 (17%)	As above (n=32)	As above (n=32)	0, 18	Pri: COPM performance and satisfaction scores, Number of falls	Between group: COPM performance (p=0.0038), satisfaction (p=0.007) Falls (p=0.036)
Miller et al.[25] 2011 *RCT*	n= 30 PPMS (n=11) SPMS (n=19) EDSS 6.5-8 Drop out: 2 (7%)	8 weeks, Domiciliary physiotherapy, 60 min, 2/week (n=15)	Wait list control (n=15)	0, 8, 16	Pri: MSIS-29 Sec: EDSS, FIM, MSQoL, MS-RS, BPI, HADA, HADD, Dynamometry, 10 m walk, timed sit to stand	Between group: R knee extensor strength(p=0.018), L knee flexor strength (p=0.006), R knee flexor strength (p=0.001), HADA (p=0.014)
Paolini et	n= 42	4 weeks: 3/week	-	0, 10, 22	Pri: MAS, FSS, Barthel	Within group:

al.[26] 2013 *RT (3 armed trial)*	All SPMS EDSS 2-6 Drop out: 0 (0%)	G1: 60 min passive movements to prevent contractures + 30-min SMV (n=14) G2: BTX-A injection 2 weeks before study then same as G1 (n=14) G3: BTX-A injection 2 weeks before study and 60 min passive movements same as G1 (n=14) §			index	G1: Knee MAS (p<0.001), ankle MAS (p<0.001), FSS (p=0.004) G2: Knee MAS (p<0.001), ankle MAS (p<0.001), FSS (p=0.05) G3: Knee MAS (p<0.001), ankle MAS (p<0.001), Both knee and ankle MAS higher at 22 weeks than 10 weeks (p<0.05), FSS (p=0.02), Barthel index (p=0.004)
Taylor et al.[28] 2013 *RT*	n= 25 All SPMS EDSS 4-6.5 Drop out: 5 (20%)	24 weeks: Weeks 1-6: peroneal FES worn in daily life, Weeks 7-12: addition of gluteal FES weeks 13-18: eight sessions of core stability physiotherapy and HEP of core stability exercises, weeks 19-24 continue with HEP FES wear continued for second 12 weeks (n=11)	Same as I but with physiotherapy and HEP first followed by FES (n=14)	-4, 0, 6, 12, 18, 24	Pri: ROGA, 10 m walk speed, MSIS-29, Falls frequency	Between group: ROGA: Without FES week 24 (p=0.044), with FES week 18 (p=0.028) Within group: I: MSIS-29 psych week 18 (p<0.05), MSIS-29 phys week 24 (p<0.05), 10 m walk speed with peroneal FES (p=0.06) and gluteal FES (p=0.06), falls frequency (p<0.05) C: 10 m walk speed with FES vs no FES (p<0.05), MSIS-29 phys week 24 (p<0.05), falls frequency (p<0.05)
Briken et al.[24] 2014 *RCT (4 armed trial)*	n= 47 PPMS (n=11) SPMS (n=31) || EDSS 4-6 Drop out: 5 (11%)	10 weeks, 15-45 min (Borg 2-3), 2-3/week Three groups: Arm ergometry (n=12), Rowing (n=12) and Cycling (n=12) §	Wait list control n=11	0, 10	Pri: VO_2 peak, 6 Min walk, VLMT, IDS, FIS	Between group: Cycle group vs C: VO_2 peak (p=0.003), 6 Min walk test (p=0.005), VLMT (p=0.009), depression (p=0.035). Arm group vs C: 6 Min walk test (p=0.003), VLMT (p=0.007), fatigue (p=0.013), IDS (p=0.001). Rowing group vs C: VLMT (p=0.001)
Skjerbaek et al.[27] 2014 *RCT*	n=11 PPMS (n=3) SPMS (n=8) EDSS 6.5-8.0 Drop out: 1 (9%)	4 weeks: 10 sessions, Endurance training: predominantly UL exercises (6 x 3 min at target heart rate (65-75% HRmax) and standard in-patient rehabilitation (n=6).	Standard in-patient rehabilitation (n=5)	0, 4	Pri: VO_2 peak, MDI, MSIS-29, 9HPT, HGT, BBT, 6minWCT	Between group: VO_2 peak (p=0.06)

Abbreviations: 6minWCT: 6 minute wheelchair test, 9HPGT: 9 hole peg test, BBT: box and block test, BDI: beck depression inventory, Borg: the borg scale of perceived exertion, BPI: brief pain inventory, C: control group, COPM: Canadian occupational performance measure, DST: double-limb support time,
FCR: flexor carpi radialis, FCU: flexor carpi ulnaris, FDS: flexor digitorum superficialis, FEV: Forced expiratory volume, FEV%: forced expiratory volume in percentage of FVC, FIM: functional independence measure, FIS: fatigue impact scale, FSS: fatigue severity scale, FVC: forced vital capacity, FVC%: forced vital capacity percentage predicted,
GHQ-12: general health questionnaire 12, HADA: hospital anxiety and depression scale anxiety sub-scale, HADD: hospital anxiety and depression scale depression sub-scale, HEP: home exercise plan, HGT: hand grip test, HRmax: heart rate max, I: intervention group, IDS: inventory of depressive symptoms, L: left, LHS: London handicap scale, m: metre, MAS: modified ashworth scale, max exp: maximal expiratory, max insp: maximal inspiratory, MDI: major depression inventory, MDT: multi-disciplinary team, min: minutes, MSIS-29: multiple sclerosis impact scale, MSIS-29 phys: multiple sclerosis impact scale physical subscale, MSIS-29 psych: multiple sclerosis impact scale psychological subscale, MSQoL: Leeds multiple sclerosis quality of life scale, n: sample size, Pri: primary outcome measures, R: right, RCT: randomised controlled trial, RE: role functioning emotional sub-scale, ROGA: Rivermead observational gait analysis, ROM: range of motion, RT: randomised trial, Sec: secondary outcome measures, SET: Tempelaar social experience checklist, SF-36: short form 36 health survey, SMV: segmental muscle vibration, UL: upper limb, VAS: visual analogue scale, VC: vital capacity, VLMT: verbal learning memory test, VO_2 peak: peak oxygen uptake.
*Baseline values of all outcome measures and final values/magnitude of changes can be found in supplementary table 1.

† Minimal acupuncture: a form of sham acupuncture where needles are inserted to a shallower depth and not at true acupuncture points (MacPherson et al., 2002).

‡ Groups did not return to baseline after 6 week washout period so analysis conducted after end of first trial.

§ Intervention group referred to as “I” throughout apart from studies by Paolini et al. and Briken et al where the three experimental arms are referred to as “G1”, “G2” and “G3” and “Arm ergometry”, “Rowing” and “Cycling” respectively.

|| Characteristic data of drop outs not supplied.

Table 4. Statistically significant results of outcome measures with available data of MCID for people with MS.

Author EDSS	Intervention	Outcome Measure (MCID)	Baseline values	Change values/ Final values
Patti et al.[22] 4-8	MDT out-patient rehabilitation	FIS (10-20 points)	**I:** 116.8 (40.9) **C:** 127.0 (36.0)	**I:** -18.8 (14.3)* **C:** 0.6 (0.9)* (*p*<0.001)†
Taylor et al.[28] 4-6.5	FES	MSIS-29 physical sub-score (8 points)	**I:** 48.8(30.6-55.0) **C:** 46.3(16.3-56.3)	**I:** 26.3(16.2-38.1)‡ (*p*<0.05)§ **C:** 35.0(21.3-51.3)‡ (*p*<0.05) §
Briken et al.[24] 4-6	Exercise therapy	6minWT (21.6 m)	**Cycling:** 288.65 m (99.3) **Arm:** 296.79 m (123.79) **Rowing:** 306.61 m (103.69) **C:** 325.92 m (117.35)	**Cycling:** 344.97(118.30)‡ **C**: 319.49(109.49)‡ (*p*=0.005)† **Arm:** 360.03(154.64)‡ **C:** 319.49 (109.49)‡ (*p*=0.003)†
		FIS (10-20 points)	**Cycling:** 35.00(18.07) **Arm:** 45.00(14.73) **Rowing:** 35.27(13.86) **C:** 38.00(15.15)	**Arm:** 31.80(11.09)‡ **C:** 39.30(17.49)‡ (*p*=0.013)†
Lo & Triche[32] Mean 4.9 (SD 1.2)	BWSTT and robot orthotics	T25fWT (17.2%)|| 6minWT (21.6 m)	**whole sample:** 9.9 s (4.2) **whole sample:** 220.3 m (96.5)	**whole sample:** -3.1(2.4)* (*p*=0.0002)§ **whole sample:** 83.4(78.0)* (*p*=0.002)§

Abbreviations: 6minWT: six minute walk test, Arm: arm ergometry group, C: control group, FIS: fatigue impact scale (maximum score: 160), I: intervention group, MCID: minimal clinically importance difference, MDT: multi-disciplinary, MSIS-29: multiple sclerosis impact scale (maximal physical sub-score: 80), T25fWT: timed 25 foot walk test

All baseline and change/final values are mean (SD)

*Change values

† Between group analysis

‡ Final values

§ Within group analysis

||17.2% improvement is a change in speed.[35] Lo & Triche presented results in seconds.[32] Means of baseline and change in speed calculated from raw time data equated to a 40% improvement in speed.

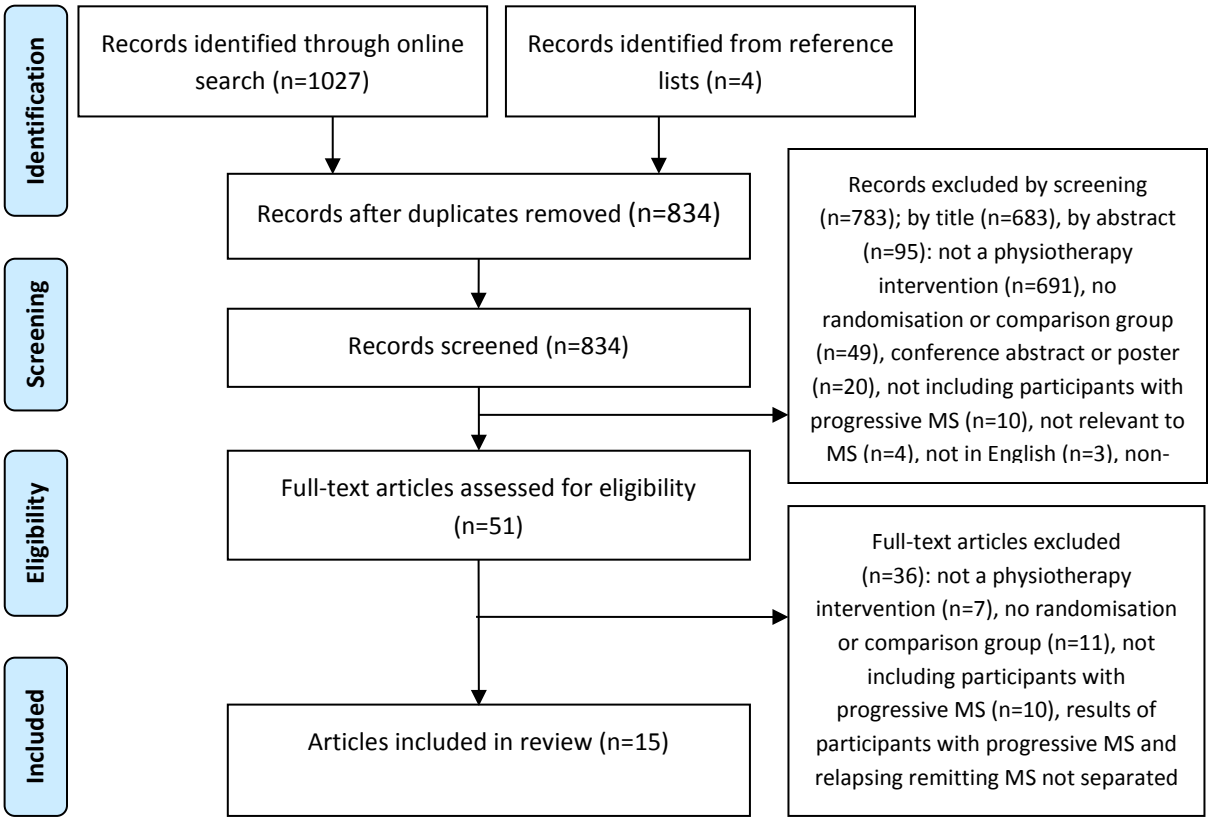

Figure 1. PRISMA flowchart of screening and inclusion process of included trials.

Supplementary table S1: Primary and secondary outcome measures with baseline values and main findings from each trial.

Author, date and design	Outcome measures and baseline values	Main findings [Intervention, Control]
Freeman et al.[33] 1997 *RCT*	**Pri:** EDSS*: **I:** 6.5(5.0-9.0), **C:** 6.5(6.0-8.5) FIM*: **I:** 67(13-87), **C:** 69.5(18-84) LHS†: **I:** 61.5(13), **C:** 66.2(8.74)	**Between group (Change values):** FIM*: motor domain: 4.0(-10,19), 2.5(-16,5) (p<0.001), Self-care domain: 1.5(-5,9), -1.0(-9,3) (p<0.0001) LHS†: 2.9 (8.9), -2.7 (8.6)(p<0.01)
Patti et al.[22] 2002 *RCT*	**Pri:** EDSS†: **I:** 6.2(1.2), **C:** 6.1(1.2) SF-36 subscales: RE†: **I:** 56.1(40.4), **C:** 42.1(43.4), PF†: **I:** 39.3(23.0), **C:** 31.2(23.1), RP†: **I:** 36.9(36.2), **C:** 26.4(36.8), BP†: **I:** 58.2(26.0), **C:** 65.4(27.1), GH†: **I:** 49.9(21.1), **C:** 45.0(20.6), VT†: **I:** 47.8(17.5), **C:** 42.7(18.4), SF†: **I:** 59.8(21.5), **C:** 57.6(27.1), MH†: **I:** 54.2 (22.8), **C:** 53.4 (23.7) **Sec:** BDI†: **I:** 11.0(7.5), **C:** 12.5(7.6) SET†: **I:** 28.9(6.0), **C:** 29.3(5.9) FIS†: **I:** 116.8(40.9), **C:** 127.0(36.0)	**Between group (Change values):** SF-36 subscales: RE†: 6.2(23.7), -0.1(0.3) (p<0.005), PF†: 6.91(18.1), -0.1(0.3) (p<0.001), RP†: 14(24.3), -0.2(0.5) (p<0.001), BP†: 14.9(20.0), -0.1(0.6) (p<0.001), GH†: 5.8(10.5), -0.2(0.5) (p<0.001), VT†: 7.4(12.5), -0.1(0.5) (p<0.001), SF†: 11.5(14.6), -0.1(0.3) (p<0.001), MH†: 7.7(15.8), -0.1(0.5) (p<0.001) BDI†: -2.2(3.4), 0.1(1.0) (p<0.001), SET†: -2.6(6.0), -0.3(0.8)(p<0.001), FIS†: -18.8(14.3), 0.6(0.9) (p<0.001)
Patti et al.[21] 2003 *RCT*	**Pri:** FIM†: **I:** 92.9(11.0), **C:** 93.7(16.4) **Sec:** EDSS†: **I:** 6.2(1.2), **C:** 6.1(1.2)	**Between group (Change values):** FIM†: 10.2(11.8): 0.0(0.7) (p<0.001)
Klefbeck and Hamrah Nedjad[31] 2003 *RCT*	**Pri:** VC (L)*: **I:** 2.4(0.5-3.4), **C:** 2.1(0.5-6.2) FVC (L)*: **I:** 2.7(1.0-3,4), **C:** 2.6(1.3-6.7) FVC%*: **I:** 78(36-93), **C:** 69(38-127) FEV (L)*: **I:** 2.2(1.0-3.3), **C:** 2.3(1.3-5.0) FEV%*: **I:** 83(82-100), **C:** 88(81-100) Max insp pressure (cmH_20)*: **I:** 42(28-74), **C:** 52(15-120) Max exp pressure (cmH_20)*: **I:** 46(36-58), **C:** 51(20-147) FSS*: **I:** 4.2(2.8-6.0), **C:** 5.1(2.0-6.7) Borg scale*: **I:** 14(9-17), **C:** 14(10-17)	**Between group (Final values):** Max insp pressure*: 67(55-100),C: 54(10-126) (p<0.01) **Within group (Final values):** **I:** max exp pressure*: 63(44-80) (p<0.02)
Baker et al.[23] 2007 *Randomised crossover design*	**Pri:** Ashworth Scale*: **whole sample:** R hip flex: 1.5(1-3), L hip flex: 2.0(1-2), R hip abd: 1.0(1-3), L hip abd: 2.0(1-2), R knee: 1.5(2-3), L knee: 2.0(2-3), R ankle: 2.0(2-3), L ankle: 2.0(2-3) Spasm frequency*: **whole sample:** R: I: 2.0(0-4), L: I: 2.0(0-4) Resting ROM in supine*: **whole sample:** R ankle: 10(10-12), L ankle: 13.5(10-15), R knee: 2.5(0-5), L knee: 2.0(0-2), R hip: 10(0-10), L hip: 20(5-20)	**Between group (Final values):** Resting ROM in supine*: R ankle: 5.0(-5-7), 10(7-12) (p=0.020), L ankle: 2.5(0-7), 10(10-15) (p=0.026), R hip: 0.0(0-5), 10(5-15) (p=0.020), L hip: 5.0(0-10), 10(5-10) (p=0.039) **Within group (Final values):** **I:** Ashworth scale*: R ankle: 2.0(1-3) (p=0.08), L ankle: 1.5(1-3) (p=0.08) **C:** spasm frequency R leg*: 1.0(0-4) (p=0.06)
Giovanelli et al.[30] 2007 *RCT*	**Pri:** MAS†: **I:** 3.63(0.49), **C:** 3.61(0.50) VAS of relief from spasticity in injected muscle, week 2: **I:** 5.18 (1.10), **C:** 5.50(1.38)	**Between group (Change values):** MAS†: -0.95(0.78), -0.28(0.46) (p<0.01) VAS of relief from spasticity in injected

		muscle†: 2.68(1.08), 1.06(1.16) (p<0.01)
Donnellan & Shanley[29] 2008 *RCT*	**Pri:** MSIS-29 phys†: **I:** 55.2(23.6), **C:** 57.7(23.8) MSIS-29 psych†: **I:** 34.3(23.7), **C:** 48.4(30.0) **Sec:** FSS†: **I:** 4.6(2.4), **C:** 2.8(1.9) GHQ-12†: **I:** 15.8(9.9), **C:** 17.7(9.5)	**Between group (Change values, C vs I):** MSIS-29 psych†: 23(21.0), 6.0(13.9) (p=0.04)
Lo & Triche[32] 2008 *Randomised crossover design*	**Pri:** EDSS†: **whole sample:** 4.9(1.2) 25 foot walk (s)†: **whole sample:** 9.9(4.2) 6 min walk (m)†: **whole sample:** 220.3(96.5) DST(%): **whole sample:** 33.2(8.0) **Sec:** step length ratio†: **whole sample:** 0.9(0.1)	**Between group (Change values):** DST†: -7.1(3.9), -1.7(3.9) (p=0.06) **Within group (Change values):** 25 foot walk†: 3.1(2.4) (p=0.0002) 6 min walk†: 83.4(78.0) (p=0.002) DST†: -5.5(4.1) (p=0.0007) EDSS†: -1.0(0.7) (p=0.001)
Barrett et al.[19] 2009 *RCT*	**Pri:** 10 m walk (ms^{-1})†: **I:** 0.79(0.35), **C:** 0.68(0.28) **Sec:** 3 min walk (m)†: **I:** 99(44), **C:** 97(44)	**Within group (Final values):** **I with FES vs I without:** 10 m walk†: 0.80(0.35) (p=0.001) 3 min walk†: 125 (55) (p=0.004) **C:** 10 m walk†: 0.77(0.29) (p=0.001) **C:** 3 min walk†: 113 (46) (p=0.005)
Esnouf et al.[20] 2010 *RCT*	**Pri:** COPM performance*: **I:** 3.5(1.75-5.0), **C:** 3.4(2.2-5.6) COPM satisfaction*: **I:** 2.2(1.0-5.0), **C:** 2.6(1.0-4.6) Number of falls: n/a	**Between group (Change values):** COPM performance*: 1.1(0.1-2.0), 0.0(0.0-0.9) (p=0.0038) COPM satisfaction*: 1.7(0.3-2.7), 0.0(0.0-1.0) (p=0.007) Number of falls (final values)*: 5, 18 (p=0.036)
Miller et al.[25] 2011 *RCT*	**Pri:** MSIS-29†: **I:** 89.9(22.8), **C:** 82.8(17.3) **Sec:** EDSS†: **I:** 7(0.5), **C:** 7.1(8.1) FIM†: **I:** 68.9(12.9), **C:** 72.2(14.2) MSQoL†: **I:** 11.9(5.3), **C:** 8.3(5.3) MS-RS†: **I:** 32.7(13.9), **C:** 27.9(9.4) BPI†: **I:** 26.7(27.7), **C:** 25.6(17.7) HADA†: **I:** 6.0(5.7), **C:** 3.1(2.1) HADD†: **I:** 5.8(3.3), **C:** 6.3(3.6) Dynamometry (kg)†: R knee ext: **I:** 10.0(5.9), **C:** 9.3(6.0), R knee flex: **I:** 9.7(5.1), **C:** 5.5(4.3), L knee ext: **I:** 7.2(5.1), **C:** 8.4(6.7), L knee flex: **I:** 7.7(6.0), **C:** 7.5(6.8) 10 m walk (s): **I:** 41.2(32.9), **C:** 43.4(27.7) timed sit to stand (s): **I:** 6.2(2.3), **C:** 5.8(3.4)	**Between group (Change values):** R knee ext strength†: 11.1(6.1), 8.4(6.7) (p=0.018) L knee flexor strength†: 6.9(5.3), 5.0(5.6) (p=0.006) R knee flexor strength†: 8.7(5.7), 4.8(4.2) (p=0.001) HADA†: 6.2(5.0), 3.8(4.0) (p=0.014)
Paolini et al.[26] 2013 *RT (3 armed trial)*	**Pri:** Knee MAS ‡: **G1:** 3(3-4), **G2:** 4(3-4), **G3:** 4(3-4) Ankle MAS‡: **G1:** 4(3-4), **G2:** 4(4-4), **G3:** 4(4-4) FSS§: **G1:** 53.6(2.31), **G2:** 43.4(3.10), **G3:** 48.5(2.77) Barthel index§: **G1:** 79.8(1.63), **G2:** 76.4(2.95), **G3:** 77.5(1.50)	**Within group (Final values):** **G1:** Knee MAS‡: 3(2-3) (p<0.001) Ankle MAS‡: 3(2-3) (p<0.001) FSS§: 46.7(2.75) (p=0.004) **G2:** Knee MAS‡: 3(2-3) (p<0.001) Ankle MAS‡:3(3-4) (p<0.001) FSS§: 39.7(2.97) (p=0.05) **G3:** Knee MAS‡: 3(2-4) (p<0.001) Ankle MAS‡: 4(3-4) (p<0.001) Knee and ankle MAS higher at 22 weeks than 10 weeks: week 10 values: Knee MAS: 3(2-3) (p<0.05), Ankle MAS: 3(3-4) (p<0.05) FSS§: 42.5(2.17)(p=0.02) Barthel index§: 77.8(1.47) (p=0.004)

Taylor et al.[28] 2013 *RT*	**Pri:** ROGA without FES‡: **I:** 13.0(8.5-21), **C:** 15(11.5-17.5) 10 m walk (ms^{-1})‡: **I:** 0.72(047-1.31), **C:** 0.82(0.51-1.01) MSIS-29 phys‡: **I:** 48.8(30.6-55.0), **C:** 46.3(16.3-56.3) MSIS-29 psych‡: **I:** 38.8(23.6-54.2), **C:** 27.2(11.1-50.0) Falls frequency‡: **I:** 23.3(8.3-67.1), **C:** 9.75(1.1-50.0)	**Between group (Final values):** ROGA‡: Without FES week 24: 11(6-14.3), 17(14.5-20) (p=0.044), with FES week 18: 10(5.3-13), 12(10-16) (p=0.028) **Within group (Final values):** **I:** MSIS-29 phys‡: 26.3(16.2-38.1) (p<0.05), MSIS-29 psych‡: week 18: 19.4(9.7-27.3) (p<0.05) 10 m walk‡: with peroneal FES: 1.2(0.72-1.27) (p=0.06), with peroneal and gluteal FES‡: 1.04(0.76-1.27)(p=0.06) Falls frequency‡: 4(3.-7.75) (p<0.05) **C:** 10 m walk with peroneal and gluteal FES vs no FES‡: 0.89(0.64-1.09) (p<0.05), MSIS-29 phys‡: 35.0(21.3-51.3) (p<0.05) Falls frequency‡: 0.5(0.0-3.075) (p<0.05)
Briken et al.[24] 2014 *RCT (4 armed trial)*	**Pri:**VO_2 peak (ml O_2.min^{-1})†: **Cycling:** 1490.18(528.20), **Arm ergometry:** 1352.30(431.26), **Rowing:** 1306.00(421.79), **C:** 1377.40(325.19) **Sec:** 6 Min walk (m)†: **Cycling:** 288.65(99.3), **Arm ergometry:** 296.79(123.79), **Rowing:** 306.61(103.69), **C:** 325.92(117.35) VLMT†: **Cycling:** 52.18(6.03), **Arm ergometry:** 46.80(10.22), **Rowing:** 51.09(10.42), **C:** 47.50(5.91) IDS†: **Cycling**: 18.36(12.27), **Arm ergometry:** 21.10(10.24), **Rowing:** 13.91(7.82), **C:** 14.10 (7.94), FIS†: **Cycling:** 35.00(18.07), **Arm ergometry:** 45.00(14.73), **Rowing:** 35.27(13.86), **C:** 38.00(15.15)	**Between group (Final values):** **Cycling vs C:** VO_2 peak†: 1253.70(297.33) (p=0.003) 6 Min walk†: 344.97(118.30), 319.49(109.49) (p=0.005), VLMT†: 62. (7.18), 51.50(8.20) (p=0.009) IDS: 14.73 (9.49), 18.40(10.36) (p=0.035) **Arm ergometry vs C:** 6 Min walk†: 360.03(154.64), 319.49 (109.49) (p=0.003) VLMT†: 58.10(8.48), 51.50(8.20) (p=0.007), FIS†: 31.80(11.09), 39.30(17.49) (p=0.013), IDS†: 12.30(6.57), 18.40(10.36) (p=0.001). **Rowing vs C:** VLMT†: 63.09(9.94), 51.50(8.20) (p=0.001)
Skjerbaek et al.[27] 2014 *RCT*	**Pri:** VO_2 peak (ml O_2.min^{-1})†: **I:** 642(209), **C:** 872(386) MDI†: **I:** 10.6(1.7), **C:** 14.6(7.3) MSIS-29†: **I:** 86(11.9), **C:** 76(20.5) 9HPGT (s)†: **I:** 36.8(13.6), **C:** 66.9(61.7) HGT (N)†: **I:** 20.3(8.7), **C:** 19.9(10.3) BBT (blocks.min^{-1})†: **I:** 23.6(8.5), **C:** 27.0(8.4) 6minWCT (m)†: **I:** 205(136), **C:** 313(71)	**Between group (Change values):** VO_2 peak†: 308(312), 2(29) (p=0.06)

Abbreviations: 6minWCT: 6 minute wheelchair test, 9HPGT: 9 hole peg test, abd: abduction, BBT: box and block test, BDI: beck depression inventory, Borg: Borg rating of perceived exertion, BP: bodily pain, BPI: brief pain inventory, C: control group, COPM: Canadian occupational performance measure, DST: double-limb support time, ext: extensor, FEV: Forced expiratory volume, FEV%: forced expiratory volume in percentage of FVC, FIM: functional independence measure, FIS: fatigue impact scale, flex: flexion, FSS: fatigue severity scale, FVC: forced vital capacity, FVC%: forced vital capacity percentage predicted, GH: general health, GHQ-12: general health questionnaire 12, HADA: hospital anxiety and depression scale anxiety sub-scale, HADD: hospital anxiety and depression scale depression sub-scale, HGT: hand grip test, I: intervention group, IDS: inventory of depressive symptoms, L: left, LHS: London handicap scale, m: metres, MAS: modified ashworth scale, max exp: maximal expiratory, max insp: maximal inspiratory, MDI:

major depression inventory, MH: mental health, min: minutes, MSIS-29: multiple sclerosis impact scale, MSIS-29 phys: multiple sclerosis impact scale physical subscale, MSIS-29 psych: multiple sclerosis impact scale psychological subscale, MSQoL: Leeds multiple sclerosis quality of life scale, PF: physical functioning, Pri: primary outcome measure, R: right, RCT: randomised controlled trial, RE: role functioning emotional, ROGA: Rivermead observational gait analysis, ROM: range of motion, RP: role physical, RT: randomised trial, s: seconds, Sec: secondary outcome measures, SET: Tempelaar social experience checklist, SF: social functioning, SF-36: short form 36 health survey, VAS: visual analogue scale, VC: vital capacity, VLMT: verbal learning memory test, VO_2 peak: peak oxygen uptake, VT: vitality.

*Values are median(range).

†Values are mean(SD).

‡Values are median(interquartile range).

§Values are mean(SE).