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Exercise therapy for multiple sclerosis (Review)

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Rietberg MB, Brooks D, Uitdehaag BMJ, Kwakkel G.
Exercise therapy for multiple sclerosis.
Cochrane Database of Systematic Reviews 2005, Issue 1. Art. No.: CD003980.
DOI: 10.1002/14651858.CD003980.pub2.

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[Intervention Review]

Exercise therapy for multiple sclerosis

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Editorial group: Cochrane Multiple Sclerosis and Rare Diseases of the CNS Group.
Publication status and date: Edited (no change to conclusions), published in Issue 10, 2015.

Citation: Rietberg MB, Brooks D, Uitdehaag BMJ, Kwakkel G. Exercise therapy for multiple sclerosis. *Cochrane Database of Systematic Reviews* 2005, Issue 1. Art. No.: CD003980. DOI: 10.1002/14651858.CD003980.pub2.

ABSTRACT

Background

No intervention has proven effective in modifying long-term disease prognosis in Multiple Sclerosis (MS) but exercise therapy is considered to be an important part of symptomatic and supportive treatment for these patients.

Objectives

To assess the effectiveness of exercise therapy for patients with MS in terms of activities of daily living and health-related quality of life.

Search methods

We searched the Cochrane MS Group Trials Register (searched: March 2004), Cochrane Central Register of Controlled Trials (CENTRAL) "The Cochrane Library Issue 2, 2004", MEDLINE (from 1966 to March 2004), EMBASE (from 1988 to March 2004), CINAHL (from 1982 to March 2004), PEDro (from 1999 to March 2004). Manual search in the journal 'Multiple Sclerosis' and screening of the reference lists of identified studies and reviews. We also searched abstracts published in proceedings of conferences.

Selection criteria

Randomised Controlled Trials (RCTs) that reported on exercise therapy for adults with MS, not presently experiencing an exacerbation; outcomes that include measures of activity limitation or health-related quality of life or both.

Data collection and analysis

Two reviewers independently extracted data and methodological quality of the included trials. Disagreements were resolved by discussion. The results were analysed using a best-evidence synthesis based on methodological quality.

Main results

Nine high-methodological-quality RCTs(260 participants) met the inclusion criteria. Six trials focussed on comparison of exercise therapy versus no exercise therapy, whereas three trials compared two interventions that both met our definition of exercise therapy. Best evidence synthesis showed strong evidence in favour of exercise therapy compared to no exercise therapy in terms of muscle power function, exercise tolerance functions and mobility-related activities. Moderate evidence was found for improving mood. No evidence was observed for exercise therapy on fatigue and perception of handicap when compared to no exercise therapy. Finally, no evidence was found that specific exercise therapy programmes were more successful in improving activities and participation than other exercise treatments. No evidence of deleterious effects of exercise therapy was described in included studies.

Authors' conclusions

The results of the present review suggest that exercise therapy can be beneficial for patients with MS not experiencing an exacerbation. There is an urgent need for consensus on a core set of outcome measures to be used in exercise trials. In addition, these studies should experimentally control for 'dose' of treatment, type of MS and should include sufficient contrast between experimental and control groups.

PLAIN LANGUAGE SUMMARY

The impact of excercise therapy for multiple sclerosis

MS is a chronic disease of the central nervous system. The variable distribution of the damage in the myelin sheath of nerves may lead to loss of strength, sensation, co-ordination and balance causing severe and progressive limitations of function in daily life. To date, there is no effective treatment for MS, however, a number of studies suggest that exercise interventions aimed to improve daily functioning of patients with MS are effective. Nine randomized controlled trials of exercise therapy for MS patients were included in this review six of which used no therapy as the comparator. There was strong evidence in favor of exercise therapy, compared to no therapy, regarding muscle function and mobility while no evidence was found of improved fatigue, in one study only. No one specifically targeted exercise program was more successful than others. No deleterious effects were described in the included studies.

BACKGROUND

Multiple sclerosis (MS) is a chronic disease of the central nervous system. The variable distribution of demyelination and axonal loss throughout the central nervous system may lead to disorders of strength, sensation, co-ordination and balance, as well as visual, cognitive and affective deficits, that may lead to severe progressive limitations of functioning in daily life. Although the exact aetiology of the disease is unknown, it is generally accepted that MS involves an abnormal immune response within the central nervous system. In Europe, at least 350,000 persons have the disease. Wide variations exist between and within European countries in the incidence of MS (3.4/100,00 between 1983 and 1987 in Western areas of Norway to 11.6/100,000 between 1979 and 1993 in western Seinäjoki, Finland) and its prevalence (38-58/100,000 in France to 144/100,000 in North-western Sardinia), as well as in the general standard of care for MS patients (Pozzilli 2002).

One of the primary aims of rehabilitation for patients with multiple sclerosis is to increase their levels of activity and participation and increase their independence (Langdon 1999). Recent advances in drug therapies, such as with ß-interferon that reduce relapse rate offer renewed hope (Anonymous 1995). However, a clinically meaningful effect of drug therapy on disability (activity) has not yet been demonstrated (Freeman 1997). Therefore, the symptomatic and supportive therapies that aim to achieve an optimisation of daily functioning of patients with MS remain important. The role of rehabilitation with physical training being a central component is perceived to be important in this process. In most cases the exercise therapy is part of a goal-orientated, multidisciplinary approach (for example Freeman 1997; Patti 2003); although, sometimes, exercise therapy is offered by one discipline only (for example Fuller 1996; Svensson 1994).

To our knowledge, the effectiveness of exercise-based rehabilitation programmes for multiple sclerosis has not been formally assessed in a systematic review. In 2001, a meta-analysis on the effectiveness of physical, psychological, and functional interventions in treating clients with multiple sclerosis was performed (Baker 2001), suggesting that occupational therapy (OT) was effective in treating the deficits in MS. However, this systematic review was not focussed on effects of exercise therapy alone, but also on the effects of other intervention regimes, such as psychotherapy and electrotherapy. In addition, pre-experimental designs without a control group were included in the analysis, which may have biased the found outcomes. Recently, a systematic review on the effectiveness of OT interventions on functional ability, social participation or health-related quality of life or both in patients with MS was performed (Steultjens 2003). No recommendations could be made on whether occupational therapy improves outcome in MS patients. The authors conclude that further research is needed, due to lack of (randomised controlled) efficacy studies. In addition, Steultjens review (Steultjens 2003) was not focused on effects of exercise therapy alone, but also examined the effects of education, advice and counselling. In addition, quasi-experimental trials (Cook 1980) were included in the analysis. This review focused only on the effects of exercise therapy for MS.

OBJECTIVES

The primary aim of the present review was to determine whether exercise therapy is an effective treatment for patients with MS in terms of Activities of Daily Living (ADL).
The secondary objective is to determine the effects of exercise therapy on health-related quality of life (HRQoL) in these patients.

METHODS

Criteria for considering studies for this review

Types of studies

The review was restricted to randomised controlled clinical trials (RCT's). RCT's are defined as trials in which investigators allocate eligible people to treatment and control group on a random basis (Clarke 2000). Randomized Cross-over trials were considered as RCT's (Clarke 2000).

Types of participants

Studies with patients, of all ages and of either sex, who fulfilled a clinical diagnosis of Multiple Sclerosis (as described by McDonald 2001; Poser 1983; Schumacher 1965) were included. For inclusion in this review the patients under research have to be free of exacerbation.

Types of interventions

All trials that fitted the authors' definition of exercise therapy were considered for inclusion. Exercise therapy was defined as: "a series of movements with the aim of training or developing the body by a routine practise or as a physical training to promote good physical health" (Webster's New World Dictionary 1982)

The goal of the exercise therapy had to be associated to one or more of the following codes of the International Classification of Functioning (ICF) (Appendix 1): code b455 (exercise tolerance functions), code d410 (changing basic body position), code d415 (maintaining a body position), code d430 (lifting and carrying objects), code d435 (moving objects with lower extremities), code d440 (fine hand use), code d445 (hand and arm use) code d450 (walking), code d455 (moving around), code d460 (moving around in different locations), code d510 (washing oneself), code d530 (toileting), code d540 (dressing), code d550 (eating), code d560 (drinking).

Therefore, the included interventions concerned studies that applied:
rehabilitation, physical therapy (with or without using training equipment), training, functional training, home physical training, and aquatic exercise. Studies were excluded if the goal of the therapy primaraly focussed on improving physical functions, but was associated with learning to handle products, technology and equipment in daily living. As a result, the following codes of the ICF-classifications were excluded: code e120 (products and technology for personal indoor and outdoor mobility and transportation), code e1151 (assistive products and technology for personal use in daily living).
In line with the above codes for exclusion, the following interventions were not incorporated in the present analysis: baths, electrotherapy, electric stimulation (functional, neuromuscular), transcutaneous electrical nerve stimulation (See Appendix 1).

Types of outcome measures

Studies that used types of outcome that measured aspects of activities limitation or HRQoL were included

Search methods for identification of studies

Electronic searches

(1) The Cochrane MS Group Specialised Register (March 2004)
(2) the Cochrane Central Register of Controlled Trials (CENTRAL) The Cochrane Library, Issue 2, 2004(Appendix 3)
(3) MEDLINE (January 1966 to March 2004)(Appendix 4)
(4) EMBASE (January 1988 to March 2004)(Appendix 5)
(5) CINAHL (from 1982 to March 2004)
(6) PEDro (from 1999 to March 2004)
(7) Dutch electronic databases PICarta and DOC-online (1999 to March 2004)

Searching other resources

In addition, a manual search in the journal 'Multiple Sclerosis' was performed. References presented in relevant publications were examined and abstracts published in proceedings of conferences were searched. The principal author of the study was contacted whenever more information about the trial was needed.

Data collection and analysis

Study selection
Two reviewers (MJCP & MBR) independently screened titles and abstracts of all studies identified by the search strategy and discarded irrelevant publications in order to create a list of eligible studies. After the potential trials had been retrieved, each reviewer independently applied the inclusion/exclusion criteria to unblinded full reports. Additional information was sought, where necessary, for all trials that appeared to meet the inclusion criteria. Consensus was used to resolve disagreements concerning the final inclusion of studies, and a third reviewer was consulted if disagreements persisted.

Methodological quality assessment
Two reviewers (DB, MBR) independently assessed the methodological quality of included trials, using an 11-items scoring list (see Appendix 2). This list contains seven criteria for internal validity and four descriptive criteria. All items were scored as clearly yes (2 points), clearly no (0 points) or not sure (1 point). Equal weight was applied to all items. Scores of individual items were summed to obtain overall score. Inter-rater agreement on methodological quality scale scores was assessed by means of the kappa statistic (Cohen 1960). The kappa coefficient ranges between zero (completely chance-explained agreement) and one (perfect agreement). A third reviewer resolved disagreements.

Data extraction
The following information was systematically extracted by the reviewers: study design, description of randomisation, characteristics of the participants (number, type of MS, disease duration, age, gender and Expanded Disability Status Scale [EDSS]-score), inclusion/exclusion criteria, description of the study and control treatment, outcome measures, length of follow up, and number of patients withdrawn or dropping out of the trial. For studies where the required data were missing, further details were requested from the main author of the manuscript.

Analysis
In order to allow for differences in applied treatment contrast, the analysis focused on comparisons of an exercise therapy intervention with a non-exercise intervention. Studies that applied exercise training for the control group as well were separated from those studies in which the control group received no exercise training. In case of comparability between two or more independent studies we pooled reported results into summary effect sizes. If a quantitative analysis was not applicable due to diversity of outcome measures, then a qualitative best-evidence synthesis was performed on the basis of the Cochrane list (see "Methodological quality of included studies Table 1"). Included studies that obtained at least 50% (or 11 out of 22 points) of the maximum feasible methodological quality score were considered to be of 'high quality', whereas studies that achieve 10 points or less on the Cochrane list were judged as 'low quality' RCTs (van Tulder 2003).

Evidence was graded into 'Strong evidence' (evidence from studies providing consistent, statistically significant findings in outcome measures in multiple high-quality RCTs), 'Moderate evidence' (evidence from studies providing at least consistent findings among multiple low-quality RCTs, or CCTs, or one high-quality RCT, or a combination of these), or 'Limited evidence' (one low-quality RCT, or CCT, or both). 'Conflicting evidence' was classified as conflicting statistically significant positive and statistically significant negative results among RCTs, or CCTs, or both. 'No evidence' was classified as no RCTs or CCTs if the number of studies showing evidence is less than 50% of the total number of retrieved studies within the same category of methodological quality (van Tulder 2003).

RESULTS

Description of studies

Electronic and manual searches identified 2593 titles and abstracts. Of these, 2570 were excluded. Reasons for exclusion were: reference to diseases or disorders of the central nervous system other than MS, reference to MS but not in combination with exercise therapy, and duplicate publications. Theses were excluded unless an article was published from it in a journal. Of the remaining 24 articles, seven met all the inclusion criteria as stated above (DeBolt 2004; Jones 1999; Lord 1998; Mostert 2002; Petajan 1996; Solari 1999; Wiles 2001). The 17 excluded trials (Craig 2003; DeSouza 1984; Di Fabio 1997; Di Fabio 1998; Freeman 1997; Freeman 1999; Fuller 1996; Gehlsen 1984; Gehlsen 1986; Ketelaer 1978; Langdon 1999; Lanzetta 2004; Patti 2003; Peterson 2001; Rodgers 1999; Svensson 1994; Wiles 2003) and details of why they failed to meet the inclusion criteria for this review are outlined in the Table of Characteristics of Excluded Studies. Freeman 1999 was discussed, but finally rejected because the objective of the trial was multi disciplinary treatment and not exercise therapy. In addition, examination of conference proceedings for unpublished and ongoing trials of exercise therapy in MS resulted in two additional RCTs (Carter 2003; O'Connell 2003). The first authors of these two RCTs then provided us with information.

The search strategy revealed nine RCTs (Carter 2003; DeBolt 2004; Jones 1999; Lord 1998; Mostert 2002; O'Connell 2003; Petajan 1996; Solari 1999; Wiles 2001) which were included in the present review. Details of the nine trials included in the present review are presented in the Table of Characteristics of Included Studies and in

the Additional Table 1. The included nine trials were conducted in five different countries (seven trials in Europe and two in the United States). All trials were published after 1995 and written in English. The included nine trials involved a total of 260 participants. Six trials contained between 20 and 50 participants (DeBolt 2004;Lord 1998; Mostert 2002; Petajan 1996; Solari 1999; Wiles 2001), whereas in three trials fewer than 20 participants were involved (Carter 2003; Jones 1999; O'Connell 2003).

Six trials (Carter 2003; DeBolt 2004; Jones 1999; O'Connell 2003; Petajan 1996; Wiles 2001), involving 164 participants, compared one or two exercise therapy interventions with a no treatment condition and three trials (Lord 1998; Mostert 2002; Solari 1999), involving 96 participants, compared two interventions that both met our criteria of exercise therapy. The study characteristics are provided in detail in the Table of Characteristics of Included Studies and in Additional Table 2.

Risk of bias in included studies

Initially methodological quality scores could not be obtained for the studies of Carter 2003 and O'Connell 2003, since only the abstracts as published in proceedings of conferences were available. The methodological quality scores of the above studies were based on additional information as provided by the first authors. Two reviewers (DB, MBR) independently assessed the methodological quality of the remaining trials. These results are presented in Additional Table 2. There was disagreement between two independent reviewers on six of the 77 criteria scored (7.8%). Cohen's kappa was 0.88. The methodological quality scores of the six included studies that investigated exercise therapy versus no exercise therapy ranged from 50% to 73% of the maximum feasible score, whereas the three studies focused on exercise therapy versus a control exercise intervention ranged from 64% to 82%. All studies were classified as high-methodological-quality RCTs. For all nine studies a summary of key indicators of internal validity is listed below.

Concealed allocation: Six studies (DeBolt 2004; Jones 1999; Lord 1998; O'Connell 2003; Solari 1999; Wiles 2001) provided some information about the method of randomisation that was used, which suggested that randomisation was probably concealed or randomisation lists were appropriately generated, or both.

Intention-to-treat analysis: Three studies (Carter 2003; O'Connell 2003; Solari 1999) stated that they had used intention-to-treat analysis.

Blinded outcome assessment: Two studies (Solari 1999; Wiles 2001) stated that they had used a blinded assessor for all outcome measures.

All studies provided information on ethical issues. All participants gave written consent and trial protocols were approved by research ethics committees.

Effects of interventions

Participant characteristics

Details are presented in the Table of Characteristics of Included Studies and in Additional Table 2 (Table 2). The participants of the studies considered in the present review all fulfilled a clinical diagnosis of Multiple Sclerosis. Most included studies describe that a neurologist assessed patients' eligibility for inclusion. Criteria for exacerbation or relapse were not defined. For trials comparing exercise therapy with no exercise therapy, the severity of the disease, as expressed by the EDSS-score, ranged from 1 to 6.5. In addition, different types of MS (benign, relapsing-remitting, secondary-progressive, progressive and chronic MS) were considered. Mean disease duration of the subjects ranged from 4.3 to 15.1 years. The mean percentage of women ranged from 30% to 83% and the mean age of the participants ranged from 34.8 to 51.6 years. For the trials comparing exercise therapy with a control exercise intervention, EDSS-scores ranged from 1 to 6.5, relapsing-remitting-, primary-progressive-, secondary-progressive- and chronic progressive MS were considered. The mean disease duration of the participants ranged from 11.2 to 18.3 years. The mean percentage of woman ranged from 48 to 85 and the mean age of the participants ranged from 44 to 54 years.

Study characteristics

Exercise therapy versus no exercise therapy

In the study of Petajan 1996, ambulatory patients with MS participated in a 15-week outpatient exercise training programme to improve measures of physical fitness and to determine its effects on ADL, mood and levels of fatigue. Patients with MS were randomly assigned to an exercise or non-exercise group. Exercise therapy consisted of 3 x 40 minute sessions per week of combined arm and leg ergometry. Of the 54 patients originally selected for the study, six were excluded for reasons unrelated to the research project and to MS. Two additional subjects were excluded secondary to an MS exacerbation. Thus, data from 46 participants were used for statistical analysis. Compared with the control group, the exercise therapy group showed statistically significant increases in maximal aerobic capacity (VO2 max.) and Physical Work Capacity (PWC) after the treatment period. For maximum isometric strength, significant differences between groups after 15 weeks of intervention were found for summed upper extremity strength (i.e., shoulder flexion, shoulder extension, elbow flexion, and elbow extension) and for summed lower extremity strength (i.e., hip extension, hip flexion, knee flexion, and knee extension). For the upper extremity three (i.e., shoulder flexion, shoulder extension, and elbow flexion) out of the four measured muscle groups reached statistically significant changes. Whereas for the lower extremity one (knee extension) out of the four measured muscle groups reached statistically significant change. Compared with the non-exercise group, the exercise therapy group improved significantly on all aspects of the physical subscale (i.e., ambulation, mobility, body care and movement) of the Sickness Impact Profile (SIP) after 10 weeks of training. After 15 weeks of training there was still a significant effect for the total score on the physical subscale (but only the mobility aspect reached significance).

Jones 1999 compared a mobility exercise programme with a weighted leg exercise training programme and with a control group receiving no exercise. Both exercise programmes were performed at home. Nineteen patients with MS were randomly allocated to the three arms of the trial. One patient of the weighted leg exercise group left the study after four weeks, due to back pain, which was believed not to be the result of the intervention. One patient of the mobility exercise group had a relapse shortly after the beginning of the study. These dropouts left 17 patients for statistical analyses. Muscle strength (MVC) of quadriceps and the functional activities walking and transferring (Timed Walk and Timed Transfer) were measured, respectively. Although the weighted leg group improved significantly on time needed for chair transfers, no significant differences were found between the three groups for gait speed, ability to transfer and muscle strength.

Wiles 2001 performed a randomised cross-over trial to determine whether physiotherapy can improve mobility in patients with chronic MS and whether there is a difference between treatments at home and in the outpatient clinic. Forty-two patients with chronic MS were randomly allocated to one of the six permutations of three-week intervals: treatments consisted of physiotherapy at home, in the outpatient clinic and no therapy. Forty patients formed the basis of the analysis, because two patients declined further assessments. No statistically significant differences were found between both exercise groups on the Rivermead Mobility Index (RMI) or any of the secondary mobility measures (i.e. balance time, timed walk, nine hole peg test, assessor global mobility change scale, VAS-patient mobility, VAS-carer mobility, and VAS-falls). Wiles 2001 reported a significant treatment effect on the primary outcome RMI when hospital or home-based physiotherapy were compared with no physiotherapy. This was corroborated by significant effects on all above-mentioned secondary measures in favour of exercise therapy compared to no exercise. In addition, statistically significant effects were found in favour of exercise therapy for mood and reduction in anxiety and depression measured with the Hospital Anxiety and Depression Scale (HADS).

In Carter 2003, 11 participants with mild to moderate MS, who were able to walk for at least four minutes, were randomly assigned to an exercise group or to a non-exercise group. The 12-week outpatient exercise-training programme consisted of twice-weekly supervised general aerobic, strengthening and flexibility exercise sessions. Of the 13 participants originally selected for the study, two were excluded before the start of the intervention, one having severe hypertension and one having developed abdominal cancer. There was a significant reduction in the normalised physiological cost index (PCI, represented by the formula: Working heart rate - Resting heart rate (beats per minute) divided by speed of walking (metres per minute) scores after 12 weeks in the exercising group, but not in the non-exercising control group. In addition, there was a significant difference between the groups in the percentage change in PCI. When comparing the exercise with the non-exercise group, significant effects were observed for isometric strength in the hip flexors and knee flexors of both limbs, the knee extensors and the ankle dorsal flexors of the right limb, but not in the ankle dorsal flexors or the knee extensors of the left limb.

O'Connell 2003 conducted a randomised controlled trial to assess the effects of an outpatient exercise therapy programme on MS patients with mild disability. Eleven participants, in the relapse-remitting stage of the disease, were randomly allocated to an exercise or non-exercise group. Exercise training consisted of twice-weekly, one hour supervised aerobic training in circuit style and once-weekly individual exercise. Two participants from the experimental group were excluded due to relapse. Following the three-month exercise training programme, the exercise group had improved significantly regarding fitness as measured with a Modified Graded Exercise Test (MGET) and quality of life as measured with the Functional Assessment of Multiple Sclerosis (FAMS) compared to baseline. The mean change in heart rate, cadence and Borg's Perception of Exertion were statistically significantly larger in favour of the exercise group when compared to the non-exercise group. No significant differences were found on the Multiple Sclerosis Impact Scale (MSIS) and gait speed.

In the study of DeBolt 2004, MS patients participated in an eight-week home-based resistance exercise programme to examine the effects on balance, leg extension power, and mobility. After stratification by disability level and age, participants were randomly assigned to an exercise or a non-exercise group. Exercise therapy consisted of resistance training (i.e., chair raises, forward lunges, step-ups, heel-toe raises, and leg curls) three times a week. The control group maintained their current level of activity. Of the 37 patients originally selected for the study, 1 was excluded secondary to an MS exacerbation. Thus, data from 36 (exercise group n = 19, and controls n = 17) participants remained for statistical analysis. After the intervention a significant difference between groups was found for leg extensor power. No between-group effects were found for exercise therapy on mobility and balance.

Exercise therapy versus a control exercise intervention

Lord 1998 used a pilot study to compare two exercise therapy approaches to improve walking in outpatients with gait disturbances due to MS. Comparison was made between a facilitation and a task-oriented approach. In total twenty-three patients with clinically stable MS were randomised; however, three participants (two from the facilitation group and one from the task group) were excluded due to a relapse or further medical intervention. Ten in each group completed the study, and were treated for a minimum of 15 treatments over a five to seven week period. Participants in both groups showed a significant overall improvement in mobility, as measured with the 10-metre timed walk, stride length, RMI and the Rivermead Visual Gait Assessment and in balance using the Berg Balance Test. No significant differences between the two exercise groups were found.

Solari 1999 assessed the efficacy of an inpatient physical rehabilitation programme on impairment (body functions and structures), disability (activities) and quality of life (QoL) of patients with MS in a randomised, single-blind controlled study. Fifty ambulatory patients with MS were assigned to three weeks of physical rehabilitation (study group) or to exercises performed at home (controls). The inpatient rehabilitation programme consisted of twice-daily exercise periods, each 45 minutes long, and included passive (stretching, mobilisation) and active interventions (for example facilitation of a normal gait pattern). Patients were evaluated at baseline, 3, 9, and 15 weeks. Five patients withdrew from the study before the end of the study period (three in the rehabilitation group: one had an exacerbation, two deteriorated clinically; two controls: one failed to present for the last examination, one deteriorated), but all were included in the analyses. No significant differences were found for impairment (body functions and structures), as measured by the Expanded Disability Status Scale (EDSS). At the end of the intervention significant differences were observed between the study group and the control group in disability (activities), as assessed by the Functional Independence Measure (FIM) motor domain and overall health-related QoL as measured with the mental composite score (emotional role-limitation, mental health, vitality and social functioning) of the SF-36. These differences remained at nine weeks.

In Mostert 2002 37 MS patients taking part in an inpatient rehabilitation programme were randomly assigned to an aerobic exercise training group or to a non-training group. The four weeks aerobic training intervention consisted of five 30 minute sessions per week of bicycle exercise with individualised intensity. The

non-exercise group took part in the normal physical therapy of the rehabilitation programme but agreed not to increase their physical activity level. Of the 37 patients originally included, 26 remained for statistical analyses. Two were excluded because of significant change in the exercise electrocardiogram . Three patients quit the study directly after random assignment to the exercise group. Two suffered from elevated spasticity of the lower extremities after testing. Of the non-exercise group, three patients had motivational problems to sustain the intervention program; two others had symptom exacerbations. Compared with baseline, the exercise group demonstrated a significant improvement of the aerobic threshold, an improvement in HRQoL (as measured with the SF-36), and an increase in activity level. However, in the present study statistical analyses were restricted to within-group comparison. Therefore, the differential effects between the groups remain inconclusive.

Best evidence syntheses

All details of outcome measures based on between-group assessments are presented in Additional Table 3 (Table 3).

Exercise therapy versus no exercise therapy

The best evidence synthesis of studies comparing exercise therapy versus no exercise therapy for MS patients was based on six RCTs (164 participants). All studies were of high methodological quality.

Strong evidence was found in favour of exercise therapy on outcome of muscle power functions (ICF code b730, see Appendix 1), as measured with maximum voluntary contraction (Jones 1999; Jones 1999), Quantitative Myometry Assessment (Carter 2003) and leg extensor power (DeBolt 2004) and exercise tolerance functions (ICF code b455), as measured by the Modified Graded Exercise Test (O'Connell 2003), Physical Work Capacity (Petajan 1996), VO2-max. (Petajan 1996), the Physiological Cost Index (Carter 2003) and the Borg's Perception of Exertion Scale (O'Connell 2003O). In addition, strong evidence was found for exercise therapy on mobility related activities (ICF codes d410 changing basic body position, d415 maintaining a body position, d450 walking, d455 moving around and d460 moving around in different locations) as measured with the Rivermead Mobility Index (Wiles 2001), timed transfer (Jones 1999), balance time (Wiles 2001) and walking cadence (O'Connell 2003).

Moderate evidence was found that exercise therapy improved hand and arm use (ICF code d445) as measured with the Nine-Hole Peg Test (Wiles 2001), and that it improved mood, as assessed with the Hospital Anxiety and Depression Scale (Wiles 2001) and the Profile of Mood States (Petajan 1996).

No evidence was found that exercise therapy has a significant effect on outcome of blood lipids, body composition and EDSS (Petajan 1996), fatigue, as measured with the Fatigue Severity Scale (Petajan 1996) and cognitive impairment, as measured with the Short Orientation-Memory-Concentration Test (Wiles 2001). In addition, no evidence was found for outcome on ADL and instrumental ADL in general. Finally, no evidence was found for exercise therapy on outcome of HRQoL, as measured with the Multiple Sclerosis Impact Scale and the Functional Assessment of Multiple Sclerosis (O'Connell 2003) and the Sickness Impact Profile (Petajan 1996).

Exercise therapy versus a control exercise intervention

Three high-methodological-quality RCTs (96 participants) compared exercise therapy with a control intervention. In all three studies the control intervention met our criteria of exercise therapy as well. Best evidence synthesis shows that there is no evidence (Lord 1998;Mostert 2002; Solari 1999) that exercise therapy is more effective than a control exercise intervention for MS patients on factors related to physical fitness (VO2-max.), mobility (gait speed, stride length, Rivermead Mobility Index, Rivermead Visual Gait Assessment, Berg Balance Test, Functional Independence Measure motor domain and Baecke Activity Questionnaire), fatigue (Fatigue severity Scale) and health related quality of life (SF-36).

DISCUSSION

This systematic review investigated the effectiveness of exercise therapy for MS patients in terms of activities of daily living and health-related quality of life. Unfortunately, statistical pooling of data was not possible mainly due to differences in measurements of outcome. Instead, a qualitative analysis using levels of evidence was performed showing strong evidence in favour of exercise therapy compared to no exercise therapy in terms of muscle power functions, exercise tolerance functions and mobility-related activities. Moderate evidence was found for improving mood. However, no evidence was observed for exercise therapy on fatigue and perception of handicap when compared to no exercise therapy. Finally, no evidence was found that specific exercise therapy programmes, including type of exercise therapy and type of setting, were superior in improving activities and participation than other exercise treatments. This latter finding suggests that the contrast of treatment between experimental and control treatment is an important element in determining the effectiveness of treatment in MS. Although the above conclusions are based on high-quality RCTs, it should be noted that most studies included a small number of patients. This lack of statistical power could have introduced type-II-error. In addition, it seems that included studies emphasised when presenting the results on the within group differences. Moreover, one study restricted the statistical analysis to within-group changes and not between-group differences (Mostert 2002).

Interestingly, only the study of Mostert 2002Mdescribes evidence of deleterious effects after testing, by means of elevated spasticity of the lower extremity in two subjects. However, no evidence of deleterious effects of exercise therapy was described by any of the nine included studies. Although in seven trials, dropouts due to an MS exacerbation were reported in groups receiving exercise training (two in Petajan 1996; one in Jones 1999; three in Lord 1998; one in Solari 1999; two in Mostert 2002; two in O'Connell 2003; one in DeBolt 2004), none of the authors of the concerned trials related these dropouts to the applied intervention. This latter finding seems to be important, because people with MS have traditionally been advised by doctors to avoid exercise therapy due to the potential effect on triggering an exacerbation or worsening disease activity. Increases in core temperature can lead to a transient increase in the frequency of clinical signs and symptoms of MS (White 2000). Acknowledging that fatigue affects the vast majority of patients, it was believed that exercise could not be tolerated and that it was preferable to focus on conserving energy. On the other hand, avoiding exercise also has its disadvantages. Sedentary people have an increased risk of developing a large number of other health problems, like obesity and cardiovascular disease. In addition, the very low activity levels observed in people with MS (Ng 1997; Stuifbergen 1997) often coincide with a loss in leisure

activities, social contacts, or normal activities of daily life, which are important for self-esteem and psychological well-being.

Participants

All participants considered in the present review fulfilled a clinical diagnosis of Multiple Sclerosis, as described by Poser 1983 or McDonald 2001. However, there was much diversity among studies with regard to patient characteristics. The large range of 1 to 6.5 in the EDSS-scores, best illustrates the diversity in severity of the disease among participants. In the studies considered different types of MS were included. However, none of the trials stratified patients on the basis of type of MS. Therefore, the effectiveness of exercise therapy for different types of MS remains indistinct in the present review. Finally, patients of all ages and of either sex were included. The percentage of female participants (64%) seems to reflect the epidemiological findings about the between-gender distribution of MS (Pozzilli 2002). The mean age of the participants ranged from 34 to 54 years. Most studies had an upper limit of 65 years of age for participants, restricting the generalisation of the present findings.

Exercise programmes

The present review did not control for 'dose' (intensity, duration and frequency) of exercise therapy. However, intensity, duration and frequency seem to be important factors in modifying treatment effects. In the present review, there was diversity among the included trials with regard to duration and frequency of training sessions, while intensity was often poorly described. Thus, it is impossible to state the best 'dose' of treatment to achieve optimal beneficial effects of exercise therapy in terms of activities and participation for patients suffering from MS. Optimum number, duration and intensity of treatment sessions all need further study.

Methodological quality of the RCTs

RCTs are generally considered to be the best paradigm of intervention research providing the strongest scientific proof of the effectiveness of an intervention (van Tulder 2003v). Most systematic reviews evaluating the effectiveness of therapeutic interventions are confined to evaluating RCTs. The methodological quality score of the RCTs included in the present review ranged from 55% to 82% of the maximum feasible score of 22 points. Even though adequate methodological approaches such as concealment of allocation, blinding of the outcome assessor, and inclusion in the analysis of all randomised participants are recognised as the most important factors in reducing bias (Schulz 1995), only one trial (Solari 1999) included in this review met all three of the above methodological criteria. In addition, reviewers were unable to obtain a methodological quality score for the studies of Carter 2003 and O'Connell 2003, since only the abstracts as published in proceedings of conferences were available. Instead, the methodological quality scores of these studies were based on information as provided by the first authors, which may have biased the results.

Outcome measures

Although some studies measured the same domains, different test protocols were used for strength, physical fitness, balance, gait speed and HRQoL, which impeded pooling of data. The large variety in outcome measures used underscores the need for a general agreement about most important measures to assess effects of exercise intervention. International consensus about a core set of outcome measures to determine the effect of exercise therapy would enable comparison of the magnitude of effect of different exercise regimens.

Potential biases of systematic reviews

Selection of all relevant studies is crucial to the validity of a systematic review. However, several biases can be introduced by the literature search and selection procedure (van Tulder 2003v). We might have missed relevant unpublished trials, which are more likely to be small studies with non-significant or negative results due to publication bias (Egger 1998). Screening references of identified trials and systematic reviews may result in an overrepresentation of positive studies in the review, because trials with a positive result are more likely to be referred to in other publications, leading to reference bias (Goetzsche 1987). The literature search was restricted to English, German, French and Dutch publications. Although reviewers acknowledge that systematic reviews should aim at inclusion of all relevant trials, independent of language, identifying trials published in any language is difficult, time consuming and costly. It is possible to include trials, of other languages, in a future update of this review.

Summary and future research

In summary, the present research synthesis suggests that exercise therapy can be beneficial for patients with MS on isometric strength, physical fitness and mobility-related ADLs such as time needed for transfer, walking cadence and balance time. In addition, positive findings were found for outcomes related to mood, such as anxiety and depression. Finally, no evidence was found that specific exercise therapy programmes were more successful in improving activities and participation than other exercise treatments. These conclusions were based on a best research evidence synthesis due to lack of comparability between measurements of outcome, acknowledging that defining the levels of evidence is essentially an arbitrary and subjective way of summarising evidence (De Vet 2003). No evidence of deleterious effects of exercise therapy were described in the identified studies.

This review provides a template for the inclusion of future trials and could be used to guide further research. It shows the need for research in older individuals, those more disabled (EDSS-score over 6.5) and those diagnosed for over 18 years. To overcome the problem of heterogeneity between subjects, future studies should stratify patients on the basis of type of MS. There is an urgent need for a general agreement about core set of measurements to be applied in MS trials investigating effectiveness of exercise therapy. Outcome measures in the activities of daily living and HRQoL domains should be included. In addition, these studies should experimentally control for 'dose' of treatment and sufficient contrast in type of intervention and adhere to the methodological principles, especially concealment of allocation, blind recording and an adequate description of the number of dropouts.

AUTHORS' CONCLUSIONS

Implications for practice

The results of this review suggest that exercise therapy, whether similar to that recommended for the healthy population or modified to simply maintain function, does have efficacy in MS. There was no evidence described of deleterious effects of exercise therapy for patients with MS and the effect of type of MS remains unclear. Based on these results, it seems reasonable to

promote exercise therapy to patients with MS not experiencing an exacerbation.

Implications for research

There is an urgent need for a consensus on a core set of measurements of outcome to be used in exercise trials. These outcome measures should be reliable and valid and reflect activities of daily living and quality of life domains. In addition, these studies should experimentally control for 'dose' of treatment and sufficient contrast in type of intervention between experimental and control groups and adhere to the methodological principles, especially concealment of allocation, blind recording and description of dropouts.

ACKNOWLEDGEMENTS

The authors would like to thank Mrs. I Wijbrands and Mr. PCW van Wieringen (PhD) for their valuable contribution to this manuscript. A special thanks to Mrs. M.J.C. Pieper and Mrs. L.M. Selhorst for their assistance on the protocol.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Carter 2003

Methods	RCT. Random assignment to exercise (EX) or non-exercise (NEX) groups
Participants	N = 11EX: N = 6, NEX: N = 5 Inclusion criteria: EDDS score of 6.0 or less, stable disease process within the last 6 weeks, able to walk for 4 minutes, full understanding of written and spoken English Exclusion criteria: acute exacerbation of MS, ongoing corticosteroid therapy, other significant medical conditions Type MS: Relapsing-remitting or secondary-progressive MS Disease duration (yr) ± SD (range): EX: 4.6 ± 1.4 (1-14), NEX: 13.8 ± 1.0 (12-18) Mean age (yr) ± SD (range): EX: 41 ± 3.2 (23-55), NEX: 44 ± 2.8 (37-53) % female: EX: 50%, NEX: 67% Mean EDSS-score ± SD: EX: 3.7 (2.0-5.5), NEX: 3.4 (2.5-5.0)
Interventions	Outpatient supervised general aerobic, strengthening and flexibility exercise sessions.Twice a week for a period of 12 weeks. In addition, subjects were encouraged to undertake one further unsupervised session per week Subjects in the non-exercise group were asked to maintain their normal activity level.
Outcomes	PCI and QMA of muscle force in lower limbs. Assessments at baseline and after 12 weeks.
Notes	Drop outs: Not when the study started , however 2 subjects were not entered due to 1 having severe hypertension and 1 developing abdominal cancer Trial presented at the World Confederation for Physical Therapy 2003 in Barcelona. Article will be submitted for publication

DeBolt 2004

Methods	RCT. Random assignment to exercise (EX) or non-exercise (NEX) groups
Participants	N = 37: EX = 19, NEX= 17 Inclusion criteria: Healthy adults with MS, ability to walk (with or without assistive devices) at least 20 m without rest Exclusion criteria: - Type MS: B,P, CP, RR Disease duration (yr) ± SD (range): EX: 15.1 ± 12.2 , NEX:13.1 ± 11.2 Mean age (yr) ± SD (range): EX: 51.6 ± 7.3, NEX: 47.8 ± 10.5 % female: EX: 79, NEX: 78 Mean EDSS-score ± SD: EX: 4.0 ± 1.8 (1-6.5), NEX: 3.5 ± 1.5 (1.5-6

DeBolt 2004 *(Continued)*

Interventions	Home-based, lower-extremity resistance training Individualised 3 times a week for 8 weeks. Mean adherence 95%. Controls Maintained current level of activity
Outcomes	Balance measured with force platform resulting in measurement of postural sway (anterior-posterior, mediolateral) and sway velocity. Leg extensor power, Up and Go test Assessments before and after the 8weeks of training
Notes	Drop outs: 1 subjects was excluded secondary to an MS exacerbation

Jones 1999

Methods	RCT. Random assignment to the no activity (NEX), general physiotherapy exercises (EX) or the weighted leg raises (WLR) groups, using sealed envelopes
Participants	N = 17: NEX= 5, EX= 6, WLR = 6 Inclusion criteria: Clinically confirmed relapsing/remitting MS, ambulant with or without the use of walking aids Exclusion criteria: Relapse of MS in the preceding 6 months Type MS: Relapsing-remitting MS Dis. dur. (yr)±SD(range): NEX: 10(2.5-20), EX: 5(1-15), WLR: 5(1.5-8) Mean age (yr) ± SD (range): NEX: 43 (36-54), EX: 49 (41-59), WLR: 38 (40-48) % female: NEX: 80, EX: 83.3, WLR: 83.3 Mean EDSS-score ± SD: ?
Interventions	EX: general mobility exercises, performed at home, with the aim of improving the patient's physical function (exercise duration and frequency similar for each person)WLR: weighted leg raises specifically to strengthen the quadriceps (5 sets of 10 leg extensions on both legs, twice a day), performed at home-EX & WLR: Mean adherence % (range)69% (45-100%) controls: Programme of supportive phone calls, but no physical intervention
Outcomes	10 and 50m Timed Walk Test (time and pulse rate), quadriceps MVC (KgF), EMG turns (turns/sec) and Timed transfer Assessments: Baseline and after 8 weeks
Notes	Drop outs: 2: 1 subject was excluded due to back pain and 1 subject was excluded due to a relapse of MS Definition MS not specified

Lord 1998

Methods	RCT. Random assignment to one of two treatment groups (facilitation approach (F) and a task-oriented approach (T)), by using sealed envelopes and block randomisation.
Participants	N = 20: F=10, T=10 Inclusion criteria: Able to walk 10m inside with or without supervision, clinically apparent relapse within 3 months before entry, clinically stable chronic progressive or relapsing-remitting MS Type MS: Chronic progressive or relapsing-remitting Dis.dur.(yr)±SD(range): F:18.3±7.0(9-28), T: 14±8.1(4-26) Mean age (yr)±SD(range): F:52.1±11(35-69),T: 54.1±8.1(43-65) % female: F: 80, T: 70 Mean EDSS-score ± SD: ?

Lord 1998 *(Continued)*

Interventions	facilitation(F) versus functional(T) out patient trainingF: reducing impairments in terms of postural control, balance responses, ability to recruit motor activity in different parts of the range, muscle length, tonus change and bony malignment by using both passive and active techniquesT: disability focused programme of functional exercises based on necessary components required for walking and functional mobilityF&T: 15-19 (one hour) treatment sessions over a period of 5-7 weeks
Outcomes	10m Timed Walk Test, RMI, RVGA, BBT and AS. Assessment at baseline and after 5-7 weeks
Notes	Drop outs: 3 drop-outs ; 2 from the facilitation group and 1 from the task group were excluded due to a relapse or further medical intervention Definition MS not specified

Mostert 2002

Methods	RCT. Random assignment to the exercise training (EX) or the non exercise (NEX) group
Participants	N= 26: EX=13, NEX =13 Inclusion criteria: Diagnosis of clinically definite MS (Poser 1983), able to pedal on a free standing bicycle ergometer Exclusion criteria: History of cardiovascular, respiratory, orthopaedic or metabolic diseases or other medical conditions, acute exacerbations of MS during at least two previous months Type MS: Relapsing-remitting, chronic-progressive or relapsing-progressive MS Disease duration (yr) ± SD (range): EX: 11.2 ± 8.5 (2-27), NEX: 12.6 ± 8.1 (2-25) Mean age (yr) ± SD (range): EX: 45.23 ± 8.66, NEX: 43.92 ± 13.90 % female: EX: 76.9, NEX: 84.6 Mean EDSS-score ± SD: EX: 4.6 ± 1.2 (2.5 - 6.5), NEX: 4.5 ± 1.9 (1 - 6.5)
Interventions	Inpatient bicycle exercise training with individualised intensity For a period of 4 weeks, 5x30-min training sessions a week Controls: Normal inpatient physiotherapy of the rehabilitation programme.
Outcomes	Kurtzke's FS, Kurtzke's EDSS, BAECKE -Activity Questionnaire, SF-36, FSS and maximal aerobic capacity Assessment at baseline and after 4 weeks
Notes	Drop outs: 12: 2 subjects quit due to motivational problems, 2 subjects were excluded due to elevated spasticity, 2 subjects were excluded because of significant ST segment change in the exercise ECG, 3 subjects decided to quit directly after random assignment to the exercise group and 3 subjects were excluded due to symptom exacerbations The study mentioned 11 dropouts instead of 12. Number of subjects in each group is 13, while in table 2 the number of subjects in the exercise groups is 12

O'Connell 2003

Methods	RCT. Random assignment to exercise (EX) or non-exercise (NEX) group
Participants	N = 11: EX = 5, NEX = 6 Inclusion criteria: Kurtzke's EDDS-score between 0 and 3, Relapse-remission stage of MS, independently mobile and static in physical ability Exclusion criteria: changes in medication and physical status over last 3 months, need for aid/appliance for mobility Type MS: Relapsing-remitting MS Disease duration (yr) ± SD (range): EX: 4.4 ± 4.5 , NEX: 4.3 ± 3.2 Mean age (yr) ± SD (range): EX: 39.4 ± 6.5 , NEX :34.8 ± 12.8 % female: EX: 40, NEX: 30

O'Connell 2003 *(Continued)*

	Mean EDSS-score ± SD: EX: (1 - 2), NEX: (1- 2.5)
Interventions	Outpatient aerobic training sessions in circuit style performed in classes.2x1h sessions in class and one session alone per week for a period of 3 months. controls: No exercise training
Outcomes	MGET, Borg's Perception of Exertion, Timed Walk (50m.), Cadence, MSIS and FAMS. Assessments at baseline and after 3 months
Notes	Drop outs: 2: 2 subjects (EX) were excluded due to a new relapse. Trial presented at the World Confederation for Physical Therapy 2003 in Barcelona. Part of a continuing trial

Petajan 1996

Methods	RCT. Random assignment to exercise (EX) or non-exercise (NEX) group.
Participants	N = 46: EX = 21, NEX = 25. Inclusion criteria: Diagnosis of clinically definite MS (Poser 1983) and Kurtzke's EDSS-score of 6.0 or less. Exclusion criteria: History of cardiovascular, respiratory, orthopaedic, metabolic or other medical conditions involvement in any form of regular physical activity for 6 months prior to the study Type MS: ? Disease duration (yr) ± SD: EX: 9.3 ± 1.6 , NEX: 6.2 ± 1.1 Mean age (yr) ± SD: EX: 41.1 ± 2.0, NEX: 39.0 ± 1.7 % female: EX: 71.4, NEX: 64.0 Mean EDSS-score ± SD: EX: 3.8 ± 0.3, NEX: 2.9 ± 0.3
Interventions	EX: Outpatient training sessions of combined arm & leg ergometry 3x40-min training sessions a week for a period of 15 weeksMean adherence 97% (91-100) NEX: No exercise training15 weeks
Outcomes	Kurtzke's FS, Kurtzke's EDSS, ISS, POMS, SIP, FSS, maximal aerobic capacity, isometric strength, blood lipids and body composition Assessments at baseline and after 5, 10 and 15 weeks
Notes	Drop outs: 8: 6 subjects were excluded for reasons unrelated to the project and MS, 2 subjects were excluded secondary to an MS exacerbation

Solari 1999

Methods	RCT. Random assignment to exercise (EX) or non-exercise (NEX) group. A stratification procedure, in relation to disease severity (EDSS-score: 3.0-4.5 and 5.0- 6.5), was undertaken before randomisation
Participants	N = 50: EX = 27, NEX = 23 Inclusion criteria: Clinically definite or laboratory supported MS (Poser ,1983), Kurtzke's EDDS-score between 3.0 and 6.5, age between 18-65 years Exclusion criteria: one or more exacerbations in the preceding 3 months, cognitive impairment (MMSE < 23.8), history of cardiovascular, respiratory, orthopaedic, psychiatric or other medical conditions, pregnancy, Treatment with immunosuppressants, interferons, 4-aminopyridine or experimental drugs in the 6 months before enrolment, rehabilitation therapy in the 3 months before admission Type MS: Relapsing-remitting, primary- progressive or secondary- progressive MS Disease duration (yr) ± SD (range): EX: 44.6 ± 10.2, NEX: 44.9 ± 10.6 Mean age (yr) ± SD (range): EX: 44.6 ± 10.2, NEX: 44.9 ± 10.6 % female: EX: 63, NEX: 48

Solari 1999 *(Continued)*

	Mean EDSS-score ± SD: 5.5 (3.0-6.5), NEX: 5.5 (3.5-7.0)
Interventions	Inpatient physical rehabilitation programme with passive and active interventions.15 weeks; 2x45-min exercise sessions a day for a period of 3 weeks, versus 12 weeks of a self-executed exercise programme at home
Outcomes	Kurtzke's EDSS, FIM, SF-36, HAI and HRSD Assessment at baseline and after 3, 9 and 15 weeks
Notes	Drop outs: 5- patients withdrew from the study before the end of the study period (3 rehabilitation: 1 had a exacerbation, 2 deteriorated clinically; 2 controls: 1 failed to present for the last examination, 1deteriorated), but all were included in the analyses Details of physical rehabilitation program have been described elsewhere (in Italian). The study is on-going. The range of EDDS-scores of the control group exceeds the 6.5 of the inclusion criteria

Wiles 2001

Methods	RCT. Random assignment to one of the 6 permutations of 3 (EX/EXH/NEX) eight week treatment periods separated by 8 week intervals, using sealed envelopes
Participants	N = 42: PT/PTH/NT: N = 42 Inclusion criteria: Diagnosis of definite or probable MS, complaining of difficulties with walking, age 18 years or older, able to walk 5m with or without a mechanical aid Exclusion criteria: Current relapse of MS, major general medical or surgical disorders, pregnancy Type MS: Chronic MS Dis. duration (yr) ± SD (range): EX/EXH/NEX: 12.3 ± 8.4 Mean age (yr) ± SD (range): EX/EXH/NEX: 47.2 (28.2-68.8) % female: EX/EXH/NEX: 64.3 Mean EDSS-score ± SD: 6.0 (4.0-6.5)
Interventions	EX: outpatient physiotherapy, with an individualised problem solving approach, focusing on specific facilitation techniques EXH: physiotherapy at home with a individualised problem solving approach, focusing on specific functional activities at home EX & EXH: twice a week (45-min) for a period of 8 weeks controls: no therapy
Outcomes	Timed Walk (6m. with one turn), NHP-test, RMI, BI, FAI, NE-ADL-I, HADS, SOMCT, VAS. Assessments 1 week before and the week after each treatment period and 8 weeks after the final treatment period
Notes	Drop outs: 2: 1 subject declined further assessment after a single treatment period and 1 subject withdrew after recruitment but before treatment

E/C, experimental vs. control group
N indicates number of patients in each group
OT: occupational therapy
PT: physiotherapy
Type MS: B = benign, C = chronic, CP = chronic progressive, RR = relapsing-remitting, SP = secundair progressive
*Only median figures given
** Only range figures given
$ Randomised crossover design,
# Only findings of the MS-groups are considered
Outcomes:
AS: Ashworth Scale
BAQ: Baecke Activity Questionnaire
BBT: Berg Balance Test
BI: Barthel Index

BPE: Borg's Perception of Exertion
EDSS: Expanded Disability Status Scale
EMG: Electromyography
FAI: Frenchay Activities Index
FAMS: Functional Assessment of Multiple Sclerosis
FIM: Functional Independence Measure
FS: Functional System scale
FSS: Fatigue Severity Scale
HADS: Hospital Anxiety and Depression Scale
HAI: Hauser's Ambulation Index
Hr-max: maximal hart rate
HRSD: Hamilton Rating Scale for Depression
ISS: Incapacity Status Scale
LHS: London Handicap Scale
MGET: Modified Graded Exercise Test
MSIS: Multiple Sclerosis Impact Scale
MSWS-12: 12 item Multiple Sclerosis Walking Scale
MVC: Maximum Voluntary Contraction
NEADL-I: Nottingham Extended Activities of Daily Living Index
NHP: Nine Hole Peg-test
PCI: Physiological Cost Index
PWC: physical Work Capacity
QMA: Quantitative Myometry assessment
POMS: Profile of Mood States
RMI: Rivermead Mobility Index
RVGA: Rivermead Visual Gait Assessment
SF-36: 36-item Short Form Health Survey Questionnaire
SIP: Sickness Impact Profile
SOMCT: Short Orientation-Memory-Concentration Test
VAS: Visual Analogue Scales
VO2-max: maximal aerobic capacity.

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

Study	Reason for exclusion
Craig 2003	Intervention is not restricted to exercise therapy
DeSouza 1984	Not a RCT
Di Fabio 1997	Not a RCT
Di Fabio 1998	Not a RCT
Freeman 1997	Not a RCT
Freeman 1999	Intervention not restricted to exercise therapy
Fuller 1996	Not a RCT
Gehlsen 1984	Not a RCT
Gehlsen 1986	Not a RCT
Ketelaer 1978	Not a RCT
Langdon 1999	Not a RCT

Study	Reason for exclusion
Lanzetta 2004	Type of subjects not restricted to MS patients
Patti 2003	Intervention not restricted to exercise therapy
Peterson 2001	Not a RCT
Rodgers 1999	Not a RCT
Svensson 1994	Not a RCT
Wiles 2003	Partecipants in this study are already included in the RCT of Wiles published in 2001

ADDITIONAL TABLES

Table 1. Methodological Quality Score

Trial	ABCDEFGHIJK	Sum score	% of maximum score	High Quality
Exercise therapy versus no exercise therapy				
Petajan 1996	11120022222	15	68	Yes
Jones 1999	21010022121	12	55	Yes
Wiles	21220012222	16	73	Yes
Carter	02020012222	13	59	Yes
O'Connell	22020002222	14	64	Yes
deBolt	10020002222	11	50	Yes
Exercise therapy versus control exercise therapy				
Lord 1998	21020022222	15	68	Yes
Solari 1999	22220022222	18	82	Yes
Mostert 2002	11020022222	17	64	Yes

Table 2. Characteristics of included studies

Reference Year	N (E/C)	Type MS	Disease duration Y	EDSS score Y	Age Y	% female	Intervention	Dose of intervention	Outcome
Petajan 1996	46 (21/25)	?	9.3/6.2	3.8/2.9	41/39	71/64	Outpatient combined arm and leg ergometry vs. No treatment	3x40 min. weekly for 15 wk	EDSS, ISS, FS, POMS, SIP, FSS,VO2-max, PWC, isometric strength, HRmax, body composition, blood lipids
Jones1999	17 (5/6/6)	RR	10/5/5	?	43/49/38	80/83/83	Home mobility exercises & home weighted leg exercise vs. No treatment	? / 5 sets of 10 leg extensions, twice a day for 8 wk.	Timed Walk, MVC, Timed Transfer, EMG
Wiles2001	42	C	12.3	6.0	47	64	PT at home vs. PT outpatient	2x45 min. weekly for 8 wk.	Timed Walk, Balance time, RMI, NHP, HADS, BI, FAI, SOMCT, VAS, NEADLI

Table 2. Characteristics of included studies *(Continued)*

							vs. No PT		
Carter 2003	11(6/5)	RR, SP	4.6/13.8	3.7/3.4	41/44	50/67	Out-patient general exercise programme vs. no exercise	Twice a week for 12 weeks	PCI, QMA
O'Connel2003	11(5/6)	RR	4.4/4.3	1.5/1.5	39.4/34.8	40/30	Out-patient aerobic training vs. n o exercise	2 x 1h in class, 1 h alone per week for 3 months	MGET, BPE, Timed Walk (50m.), Cadence, MSIS and FAMS
DeBolt2004	37(19/17)	B, RR, P, CP	15.1/13.1	4.0/3.5	51.6/47.8	79/78	Home-based resistance exercise vs. No treatment	3 times a week for 8 weeks	Balance met postural sway & sway velocity, Leg extensor power, up and Go test
Exercise therapy versus control									

Table 2. Characteristics of included studies *(Continued)*

exercise therapy									
Lord 1998	20 (10/10)	CP, RR	14.0/18.3	?	54/52	70/80	Outpatient task-oriented training vs. facilitation training	15-19 / 16-19 (1h) sessions in 5-7 wk.	Timed Walk, RMI, RVGA, BBT, Stride length
Solari 1999	50 (27/23)	RR, PP, SP	16.6/13.3	5.5/5.5	45/45	63/48	Inpatient physical rehabilitation vs. Home performed exercises	2x45 min¤ daily vs. self-executed exerc. for 3 wk	SF-36, FIM, EDSS, HAI, HRSD
Mostert 2002	26 (13/13)	CP, RR, RP	11.2/12.6	4.6/4.5	45/44	77/85	Inpatient bicycle training vs. inpatient PT	5x30 min. weekly for 3-4 wk.	FS, EDSS, BAQ, SF-36, FSS, VO2-max,

Table 3. Between group effects of included trials (BGE)

Study	Impairment	BGE	Activities	BGE	Participation	BGE
Exercise therapy versus no exercise therapy						
Petajan1996 Combined arm & leg ergometry vs. no exercise	Physical Work capacity VO2-max S MVC UE & LE Blood Lipids Body composition EDSS & FS FS Bowel/Bladder score	+ + + - - - +	ISS	-	POMS FSS SIP Physical sub scale SIP Psychosocial sub scale	- - + -
Jones 1999 Weighted leg exercise vs.Mobility exercise vs. No exercise	EMG MVC Quadriceps	- -	Timed walk 10&50 m. Timed transfer	- + (1)		
Wiles 2001 Exercise therapy at home vs.Exercise therapy in hospital vs.None treatment group	SOMCT	-	Balance time Timed Walk RMI VAS mobility NHP mob. UE NHP mob. UE BI FAI NE-ADL-I	+ (2) + (2) + (2) + (2) - (3) + (4) ? nrr nrr	HADS anxiety HADS depression	+ (2) + (2)
Carter 2003 General exercise vs. non-exercise	PCI QMA	+ +				
O'Connell, 2003 Aerobic training exercise vs. non-exercise	HR BPE MGET	+ + -	Timed Walk 50 m. Cadence	- +	MSIS FAMS	- -
DeBolt 2004 Resistance training vs. no treatment	Leg extensor power	+	Up and Go test Postural sway Sway velocity	- - -		
Exercise therapy versus a control exercise intervention						
Lord 1998 Facilitation exercise vs.task orientated exercise			Timed walk 10 m. Stride length RMI RVGA Berg Balance test	- - - - -		
Solari 1999 Physical rehab.vs. exercise performed at home	EDSS	-	FIM motor domain at 3 & 9 weeks	+ (5)	SF-36 MCS at 3 & 9 wk SF-36 PCS at 3 & 9 wk SF-36 MCS	+ (5) - - -

Table 3. Between group effects of included trials (BGE) *(Continued)*

					at 15 wk SF-36 PCS at 15 wk	
Mostert 2002 Bicycle exercise vs. normal physical therapy	VO2-max	nrr	BAQ	nrr	FSS SF-36	nrr nrr

BGE indicates between groups effect in each group
+ = significant between groups effect in favour of exercise therapy intervention
- = non -significant between groups effect
nrr = no results reported
vs. = versus
UE: upper extremity
LE: lower extremity
(1)for weighted leg exercise group as compared to mobility exercise and no exercise
(2)comparing hospital or home-based physiotherapy with no physiotherapy
(3)comparing home-based physiotherapy with no physiotherapy
(4)comparing hospital-based physiotherapy with no physiotherapy
(5)for physical rehabilitation group as compared to exercise performed at home.

Outcomes:
BAQ: Baecke Activity Questionnaire
BBT: Berg Balance Test
BI: Barthel Index
BPE: Borg's Perception of Exertion
EDSS: Expanded Disability Status Scale
EMG: Electromyography
FAI: Frenchay Activities Index
FAMS: Functional Assessment of Multiple Sclerosis
FIM: Functional Independence Measure
FS: Functional System Scale
FSS: Fatigue Severity Scale
HADS: Hospital Anxiety and Depression Scale
ISS: Incapacity Status Scale
LHS: London Handicap Scale
MGET: Modified Graded Exercise Test
MSIS: Multiple Sclerosis Impact Scale
MVC: Maximum Voluntary Contraction
NEADL-I: Nottingham Extended Activities of Daily Living Index
NHP: Nine Hole Peg-test
PCI: Physiological Cost Index
POMS: Profile of Mood States; PhCS.: Physical Composite Score & MCS: Mental Composite Score
QMA: Quantitative Myometry Assessment
RMI: Rivermead Mobility Index
RVGA: Rivermead Visual Gait Assessment
SF-36: 36 item Short Form Health Survey Questionnaire
SIP: Sickness Impact Profile
SOMCT: Short Orientation-Memory-Concentration Test
VAS: Visual Analogue Scales
VO2-max: maximal aerobic capacity.

APPENDICES

Appendix 1. International Classification of Functions coding

b455 Exercise tolerance functions

Functions related to respiratory and cardiovascular capacity as required for enduring physical exertion.
Inclusions: functions of physical endurance, aerobic capacity, stamina and fatigability
Exclusions: functions of the cardiovascular system; haematological system functions; respiration functions; respiratory muscle functions; additional respiratory functions
b455 Exercise tolerance functions
>b455 Exercise tolerance functions
>b4550 General physical endurance
>b4551 Aerobic capacity
>b4552 Fatigability
>b4558 Exercise tolerance functions, other specified
>b4559 Exercise tolerance functions, unspecified

Neuromusculoskeletal and movement-related functions
+ Functions of the joints and bones (b710-b729)
+ b710 Mobility of joint functions
+ b715 Stability of joint functions
+ b720 Mobility of bone functions

> b729 Functions of the joints and bones, other specified and unspecified
+ Muscle functions (b730-b749)
+ b730 Muscle power functions
+ b735 Muscle tone functions
+ b740 Muscle endurance functions
> b749 Muscle functions, other specified and unspecified

+ Movement functions (b750-b789)
+ b750 Motor reflex functions
> b755 Involuntary movement reaction functions
+ b760 Control of voluntary movement functions
+ b765 Involuntary movement functions
> b770 Gait pattern functions
+ b780 Sensations related to muscles and movement functions
> b789 Movement functions, other specified and unspecified functions (b750-b789)
> b798 Neuromusculoskeletal and movement-related functions, other specified
> b799 Neuromusculoskeletal and movement-related functions, unspecified

d410 Changing basic body position
Getting into and out of a body position and moving from one location to another, such as getting up out of a chair to lie down on a bed, and getting into and out of positions of kneeling or squatting.
Inclusion: changing body position from lying down, from squatting or kneeling, from sitting or standing, bending and shifting the body's centre of gravity
Exclusion: transferring oneself
+d410 Changing basic body position
>d410 Changing basic body position
>d4100 Lying down
>d4101 Squatting
>d4102 Kneeling
>d4103 Sitting
>d4104 Standing
>d4105 Bending
>d4106 Shifting the body's centre of gravity
>d4108 Changing basic body position, other specified
>d4109 Changing basic body position, unspecified

d415 Maintaining a body position
Staying in the same body position as required, such as remaining seated or remaining standing for work or school.
Inclusions: maintaining a lying, squatting, kneeling, sitting and standing position
+d415 Maintaining a body position
>d415 Maintaining a body position
>d4150 Maintaining a lying position
>d4151 Maintaining a squatting position
>d4152 Maintaining a kneeling position
>d4153 Maintaining a sitting position

>d4154 Maintaining a standing position
>d4158 Maintaining a body position, other specified
>d4159 Maintaining a body position, unspecified

d430 Lifting and carrying objects
Raising up an object or taking something from one place to another, such as when lifting a cup or carrying a child from one room to another.
Inclusions: lifting, carrying in the hands or arms, or on shoulders, hip, back or head; putting down
+d430 Lifting and carrying objects
>d430 Lifting and carrying objects
>d4300 Lifting
>d4301 Carrying in the hands
>d4302 Carrying in the arms
>d4303 Carrying on shoulders, hip and back
>d4304 Carrying on the head
>d4305 Putting down objects
>d4308 Lifting and carrying, other specified
>d4309 Lifting and carrying, unspecified

d435 Moving objects with lower extremities
Performing co-ordinated actions aimed at moving an object by using the legs and feet, such as kicking a ball or pushing pedals on a bicycle.
Inclusions: pushing with lower extremities; kicking
d435 Moving objects with lower extremities
+d435 Moving objects with lower extremities
>d4350 Pushing with lower extremities
>d4351 Kicking
>d4358 Moving objects with lower extremities, other specified
>d4359 Moving objects with lower extremities, unspecified

d440 Fine hand use
Performing the co-ordinated actions of handling objects, picking up, manipulating and releasing them using one's hand, fingers and thumb, such as required to lift coins off a table or turn a dial or knob.
Inclusions: picking up, grasping, manipulating and releasing
Exclusion: lifting and carrying objects
>d440 Fine hand use
>d4400 Picking up
>d4401 Grasping
>d4402 Manipulating
>d4403 Releasing
>d4408 Fine hand use, other specified
>d4409 Fine hand use, unspecified

d445 Hand and arm use
Performing the co-ordinated actions required to move objects or to manipulate them by using hands and arms, such as when turning door handles or throwing or catching an object Inclusions: pulling or pushing objects; reaching; turning or twisting the hands or arms; throwing; catching
Exclusion: fine hand use
>d445 Hand and arm use
>d445 Hand and arm use
>d4450 Pulling
>d4451 Pushing
>d4452 Reaching
>d4453 Turning or twisting the hands or arms
>d4454 Throwing
>d4455 Catching
>d4458 Hand and arm use, other specified
>d4459 Hand and arm use, unspecified

d450 Walking
Moving along a surface on foot, step by step, so that one foot is always on the ground, such as when strolling, sauntering, walking forwards, backwards, or sideways.
Inclusions: walking short or long distances; walking on different surfaces; walking around obstacles
Exclusions: transferring oneself; moving around
>d450 Walking

>d4500 Walking short distances
>d4501 Walking long distances
>d4502 Walking on different surfaces
>d4503 Walking around obstacles
>d4508 Walking, other specified
>d4509 Walking, unspecified

d455 Moving around
Moving the whole body from one place to another by means other than walking, such as climbing over a rock or running down a street, skipping, scampering, jumping, somersaulting or running around obstacles.
Inclusions: crawling, climbing, running, jogging, jumping, and swimming
Exclusions: transferring oneself; walking
+d455 Moving around
>d455 Moving around
>d4550 Crawling
>d4551 Climbing
>d4552 Running
>d4553 Jumping
>d4554 Swimming
>d4558 Moving around, other specified
>d4559 Moving around, unspecified

d460 Moving around in different locations
Walking and moving around in various places and situations, such as walking between rooms in a house, within a building, or down the street of a town.
Inclusions: moving around within the home, crawling or climbing within the home; walking or moving within buildings other than the home, and outside the home and other buildings
+d460 Moving around in different locations
>d460 Moving around in different locations
>d4600 Moving around within the home
>d4601 Moving around within buildings other than home
>d4602 Moving around outside the home and other buildings
>d4608 Moving around in different locations, other specified
>d4609 Moving around in different locations, unspecified

d510 Washing oneself
Washing and drying one's whole body, or body parts, using water and appropriate cleaning and drying materials or methods, such as bathing, showering, washing hands and feet, face and hair, and drying with a towel.
Inclusions: washing body parts, the whole body; and drying oneself
Exclusions: caring for body parts; toileting
+d510 Washing oneself
>d510 Washing oneself
>d5100 Washing body parts
>d5101 Washing whole body
>d5102 Drying oneself
>d5108 Washing oneself, other specified
>d5109 Washing oneself, unspecified

d530 Toileting
Planning and carrying out the elimination of human waste (menstruation, urination and defecation), and cleaning oneself afterwards.
Inclusions: regulating urination, defecation and menstrual care
Exclusions: washing oneself; caring for body parts
+d530 Toileting
>d530 Toileting
>d5300 Regulating urination
>d5301 Regulating defecation
>d5302 Menstrual care
>d5308 Toileting, other specified
>d5309 Toileting, unspecified

d540 Dressing

Carrying out the co-ordinated actions and tasks of putting on and taking off clothes and footwear in sequence and in keeping with climatic and social conditions, such as by putting on, adjusting and removing shirts, skirts, blouses, pants, undergarments, saris, kimono, tights, hats, gloves, coats, shoes, boots, sandals and slippers.
Inclusions: putting on or taking off clothes and footwear and choosing appropriate clothing.
+d540 Dressing
>d5400 putting on clothes
>d5401 Taking off clothes
>d5402 Putting on footwear
>d5403 Taking off footwear
>d5404 Choosing appropriate clothing
>d5408 Dressing, other specified
>d5409 Dressing, unspecified

d550 Eating
Carrying out the co-ordinated tasks and actions of eating food that has been served, bringing it to the mouth and consuming it in culturally acceptable ways, cutting or breaking food into pieces, opening, bottles and cans, using eating implements, having meals, feasting or dining.
Exclusion: drinking

Appendix 2. Assessment of methodological quality of included trials

A: Was the assigned treatment adequately concealed prior to allocation?
2 = method did not allow disclosure of assignment
1 = small but moderate change of disclosure of assignment or unclear
0 = quasi-randomised or open list/tables
B: Were the outcomes of participants who withdrew or were excluded after allocation described and included in an 'intention to treat' analysis?
2 = withdrawals well described and accounted for in analysis
1 = withdrawals described and analysis is not possible
0 = no mention, inadequate mention, or obvious differences and no adjustment
C: Were the outcome assessors blind to assignment status?
2 = effective action taken to blind the assessors
1 = small or moderate chance of unblinding of assessors
0 = not mentioned or not possible
D: Were the treatment and control group, or in case of more treatment groups the treatment groups, comparable at entry?
2 = good comparability of groups
1 = confounding is small, but mentioned
0 = large potential for confounding, or not mentioned
E: Were the participants blind to assignment status following allocation?
2 = effective action taken to blind the participants
1 = small or moderate chance of unblinding of participants
0 = not mentioned or not possible
F: Were the treatment providers blind to assignment status?
2 = effective action taken to blind the treatment providers
1 = small or moderate chance of unblinding of treatment providers
0 = not mentioned or not possible
G: Were care programmes, other than the trial options, identical?
2 = care programmes clearly identical
1 = clear but trivial differences
0 = not mentioned or clear and important differences in care programmes
H: Were the inclusion and exclusion criteria for entry clearly defined?
2 = clearly defined
1 = inadequately defined
0 = not defined
I: Were the interventions clearly defined?
2 = clearly defined interventions are applied with a standardised protocol
1 = clearly defined interventions are applied but the applied protocol is not standardised
0 = intervention and/or application protocol are poorly or not defined
J: Were the outcome measures used clearly defined?
2 = clearly defined
1 = inadequately defined
0 = not defined
K: Were diagnostic tests used in outcome assessment clinically useful?

2 = optimal
1 = adequate
0 = not defined, not adequate

Appendix 3. CENTRAL search strategy

#1"multiple sclerosis"
#2MeSH descriptor Multiple Sclerosis explode all trees
#3"Demyelinating disease*"
#4MeSH descriptor Demyelinating Diseases, this term only
#5"transverse myelitis"
#6MeSH descriptor Myelitis, Transverse, this term only
#7"neuromyelitis optica"
#8"optic neuritis"
#9MeSH descriptor Optic Neuritis explode all trees
#10"encephalomyelitis acute disseminated"
#11MeSH descriptor Encephalomyelitis, Acute Disseminated, this term only
#12"devic"
#13(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)
#14MeSH descriptor Physical Therapy Modalities explode all trees
#15MeSH descriptor Exercise Movement Techniques explode all trees
#16MeSH descriptor Movement explode all trees
#17MeSH descriptor Physical Fitness explode all trees
#18MeSH descriptor Occupational Therapy, this term only
#19MeSH descriptor Physical Endurance explode all trees
#20MeSH descriptor Physical Stimulation, this term only
#21MeSH descriptor Physical Education and Training explode all trees
#22MeSH descriptor Physical Medicine, this term only
#23MeSH descriptor Exercise explode all trees
#24'physical therapy' or 'exercise movement techniques' or 'occupational therapy' or (movement) or 'physical fitness'
#25'physical endurance' or 'physical stimulation' or 'physical education' or 'physical training' or (exercise)
#26MeSH descriptor Rehabilitation, this term only
#27MeSH descriptor Quality of Life, this term only
#28relaxation OR therapy OR "recovery of function"
#29(#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28)
#30(#13 AND #29)

Appendix 4. MEDLINE (PubMed) search strategy

((("physical endurance") OR ("physical stimulation") OR ("physical education") OR ("physical training") OR (exercise) OR (therapy) OR (relaxation) OR ("physical therapy" OR "exercise movement techniques" OR "occupational therapy" OR movement OR "physical fitness") OR ("recovery of function")) OR ("Physical Therapy Modalities"[mh] OR "Physical Therapy (Specialty)"[mh:noexp] OR "Exercise Movement Techniques"[mh] OR "Occupational Therapy"[mh:noexp] OR "Movement"[mh] OR "Physical Fitness"[mh:noexp] OR "Physical Endurance"[mh] OR "Physical Stimulation"[mh:noexp] OR "Physical Education and Training"[mh] OR "Physical Medicine"[mh:noexp] OR "Exercise"[mh] OR "Rehabilitation"[mh:noexp] OR "Quality of Life"[mh:noexp])) AND ((((("Multiple Sclerosis"[mh]) OR ("Myelitis, Transverse"[mh:noexp]) OR ("Demyelinating Diseases"[mh:noexp]) OR ("Encephalomyelitis, Acute Disseminated"[mh:noexp]) OR ("Optic Neuritis"[mh])) OR ((("multiple sclerosis") OR ("neuromyelitis optica") OR ("transverse myelitis") OR (encephalomyelitis) OR (devic) OR ("optic neuritis")) OR ("demyelinating disease*") OR ("acute disseminated encephalomyelitis"))) AND (((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomized[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) NOT ((animals[mh]) NOT ((animals[mh]) AND (human[mh])))))

Appendix 5. EMBASE search strategy

((((('encephalomyelitis'/exp) OR ('demyelinating disease'/exp) OR ('multiple sclerosis'/exp) OR ('myelooptic neuropathy'/exp) OR ('multiple sclerosis':ti,ab) OR ('neuromyelitis optica':ti,ab) OR (encephalomyelitis:ab,ti) OR (devic:ab,ti)) AND (('crossover procedure'/exp) OR ('double blind procedure'/exp) OR ('single blind procedure'/exp) OR ('randomized controlled trial'/exp) OR (random*:ab,ti) OR (factorial*:ab,ti) OR (crossover:ab,ti) OR (cross:ab,ti AND over:ab,ti) OR (placebo*:ab,ti) OR ('double blind':ab,ti) OR ('single blind':ab,ti) OR (assign*:ab,ti) OR (alloact*:ab,ti) OR (volunteer*:ab,ti))) AND ((('physiotherapy'/exp) OR ('kinesiotherapy'/exp) OR ('occupational therapy'/exp) OR ('movement'/exp) OR ('fitness'/exp) OR ('endurance'/exp) OR ('stimulation'/exp) OR ('physical education'/exp) OR ('physical medicine'/exp) OR ('exercise'/exp)) OR ((exercise:ab,ti) OR ('physical therapy modalities':ab,ti) OR (physiotherapy:ab,ti) OR ('exercise movement techniques':ab,ti) OR ('occupational therapy':ab,ti) OR (movement:ab,ti) OR ('physical fitness':ab,ti) OR ('physical endurance':ab,ti) OR ('physical stimulation':ab,ti) OR ('physical education':ab,ti) OR ('physical training':ab,ti) OR ('physical medicine':ab,ti))) AND [humans]/lim AND [embase]/lim

FEEDBACK

Exercise therapy for multiple sclerosis

Summary

Some neglected problems dog the rehabilitation in MS: Patients may suffer longer periods of visual loss, fatigue and other incapacitations after definite efforts.
They show periventricular lesion formations whose dynamics can only be explained by local physical impacts: http://www.med.harvard.edu/AANLIB/cases/case5/mr2/020.html.The possibility of producing corresponding impacts by stronger efforts (www.ms-info.net) deserves more attention.
All this provokes the question whether, in training MS patients, there ought not to be paid more attention to the point whether this training does entail a propagation of extracranial venous pressure excesses into the affected parts of the brain.
Hoping not to appear all to burdensome in raising this issue, but I would greatly appreciate to learn something about your ideas in this respect.

Reply

Thank you for your reaction on our review 'Exercise therapy for multiple sclerosis'. The question you are raising is interesting. However, based on our review we can't provide an answer to this question. To our knowledge there is no direct evidence for your hypothesis. We are not aware of any report of harm from exercise. Further research is needed to determine the effects of exercise therapy on extra cranial venous pressure and the affected parts of the brain.

Contributors

Comment received from: Franz Schelling - January 2006
Reply from: Marc Rietberg, Dina Brooks, Bernard Uitdehaag, Gert Kwakkel (Review authors) - January 2006
Processed by: Dean Marko Wingerchuk (Feedback Editor) - January 2006

Evidence of efficacy of exercise therapy, 9 July 2009

Summary

In your qualitative review, when considering the three studies comparing "exercise therapy" to a control intervention, you reported that there was no evidence of efficacy of "exercise therapy" for the FIM motor domain (Results page 12, and Discussion page 14). On the opposite, there was a significant effect at the end of treatment (3 weeks) which persisted at nine weeks (Solari et al., Neurology 1999). The same was for the SF-36 mental composite score.

Reply

We appreciate your feedback on our review ‘exercise therapy for multiple sclerosis’. The issue that you remind us of is interesting and seems to be conflicting in the present review. We acknowledge the found results in your study (Solari 1999) in favour of the physical rehabilitation group on the FIM motor domain, and SF-36 mental composite score. Those results are presented in the results section of our review (study characteristic on page 9, and Table 3. Between group effects on page 11 and 12).

However, it is important to note that we did apply a best (research) evidence syntheses (BES) in our review. For that we defined different categories for evaluation at different levels of ICF. As shown in our systematic review, physical fitness was measured by VO2-max, and mobility by outcomes such as gait speed, stride length, Rivermead Mobility Index, Rivermead Visual Gait Assessment, Berg Balance Test, Functional Independence Measure motor domain and Beacke Activity Questionnaire. Health related quality of life (HrQoL) was measured by SF-36.

Best evidence syntheses of the category ‘mobility’ did reveal the classification ‘no evidence’, because the number of studies showing evidence is less than 50% of the total number of studies within the same category of methodological quality.

Best evidence syntheses of the category ‘Health related quality of life’ was classified as ‘no evidence’. Your study reported a between group effect on the MCS of the FS-36 at 3 and 9 weeks, the study of Mostert (2002), however, did not report between group effects. Within that, the outcome of HrQoL after BES remains inconclusive.

Since 2004, new RCTs on exercise therapy for MS have been published and, recently, we started making an update of our review. In this update, we will reconsider above mentioned points addressed by you and we will reconsider a meta-analysis of pooled outcomes. Otherwise we will stick by applying a best evidence synthesis. Hopefully, the update will allow us to publish more straightforward conclusions with respect to effects of exercise therapy in patients with MS.

Contributors

Comment received from: Alessandra Solari - June 2009

Reply from: Marc Rietberg, Dina Brooks, Bernard Uitdehaag, Gert Kwakkel (Review authors) - July 2009
Processed by: Dean Marko Wingerchuk (Feedback Editor) - July 2009

WHAT'S NEW

Date	Event	Description
22 November 2010	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 4, 2002
Review first published: Issue 1, 2005

Date	Event	Description
9 July 2009	Feedback has been incorporated	Feedback from A Solari added along with reply from the authors
25 June 2008	Amended	Converted to new review format.
23 January 2006	Feedback has been incorporated	Feedback from F Schelling added along with reply from the authors

CONTRIBUTIONS OF AUTHORS

M. Rietberg is author of the review, G. Kwakkel the supervisor. D.Brooks took part in rating the methodological quality. D. Brooks and B.Uitdehaag critically reviewed the manuscript. All reviewers discussed, the protocol, data collection, results and conclusions.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- The VU University Medical Centre covered expenses and provided access to electronic databases and internet for identification of studies, Netherlands.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

*Exercise Therapy; *Quality of Life; Multiple Sclerosis [*rehabilitation]; Randomized Controlled Trials as Topic

MeSH check words

Humans