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The effect of exercise therapy on fatigue in multiple sclerosis

AK Andreasen[1], E Stenager[2,3] and U Dalgas[4]

Abstract

Background: Fatigue occurs in the majority of patients with multiple sclerosis (MS) and therapeutic possibilities are few. Exercise therapy is a therapeutic option but no studies have systematically reviewed the existing literature evaluating the effect of exercise therapy on MS fatigue.

Objective: To determine the effect of exercise therapy on MS fatigue by systematically reviewing the literature.

Methods: A comprehensive literature search (PubMed, SweMed +, Embase, Cochrane, CINAHL, PEDro, Sport Discuss and Bibliotek.dk) was conducted.

Results: Studies evaluating the effect of exercise therapy on MS fatigue show heterogeneous results and only few studies have evaluated MS fatigue as the primary outcome. The heterogeneous findings seem to be related to the selected study population, which in many studies are non-fatigued. Most studies that have included fatigued patients with MS show positive effects, although it is not clear whether any exercise modalities are superior to others because there are no comparative studies regarding different exercise interventions.

Conclusion: Exercise therapy has the potential to induce a positive effect on MS fatigue, but findings are heterogeneous probably because many studies have applied non-fatigued study populations. Furthermore, only few studies have evaluated MS fatigue as the primary outcome measure, emphasizing the need for future studies within this field.

Keywords

exercise, training, combined training, endurance training, fatigue, multiple sclerosis, resistance training, strength training

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Introduction

Multiple sclerosis (MS) fatigue is defined as ‘a lack of physical and/or mental energy that is perceived by the individual or the caregiver to interfere with usual and desired activities’.[1] It is a frequent symptom, with 75% of patients with MS perceiving fatigue persistently or sporadically during a 2-year period.[2] Also, 55% of all MS patients describe it as one of their worst symptoms.[3] When fatigue is a direct consequence of MS it is termed ‘primary’ fatigue, whereas that caused by MS-related conditions such as infection, poor sleep, spasticity, pain and drug side effects is termed ‘secondary’ fatigue. A recent review concluded that the effectiveness of both pharmacological and psychosocial/psychological interventions in counteracting MS fatigue is at best modest, and is often absent.[4] Interventions combating MS fatigue are, therefore, highly warranted. An efficient rehabilitation strategy is exercise therapy, but its role in MS rehabilitation has been a controversial issue. For years, patients with MS were advised not to participate in exercise because it was reported to lead to worsening of symptoms or fatigue.[5] During the past decades, however, studies on exercise therapy in MS have shown

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[1]Department of Neurology, Rigshospitalet, Denmark.
[2]MS-clinic of Southern Jutland (Soenderborg, Vejle, Esbjerg). Department of Neurology, Soenderborg Hospital, Denmark.
[3]Institute of Regional Health Services, University of Southern Denmark, Denmark.
[4]Department of Sport Science, Aarhus University, Denmark.

Corresponding author:
Anne Katrine Andreasen, Department of Neurology, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark
Email: ak@ki.au.dk

promising effects.[6] Recently, it has been suggested that exercise in general possesses the potential to reduce MS fatigue.[7]

In this review, a systematic literature search on this specific topic is presented. The aim is to identify studies that evaluate the effect of exercise on self-reported fatigue in patients with MS.

Methods

The present review is based on a comprehensive literature search (PubMed, SweMed+, Embase, Cochrane, CINAHL, PEDro, Sport Discuss and Bibliotek.dk). In PubMed the search was performed using the MeSH terms 'Musculoskeletal Physiological Processes' or 'Physical Therapy Modalities' or 'training' or 'exercise' in combination with 'multiple sclerosis' and 'fatigue'. In the other databases the exercise-related terms were 'physical therapy', 'physical activity', 'training', 'athletic training' or 'exercise' again in combination with 'multiple sclerosis' and 'fatigue'. The search was conducted on the 7th of July 2010. In Embase the search was limited to studies published in or after 1989, as this is the year the first MS-specific fatigue scale was published, the Fatigue Severity Scale (FSS).[8] Otherwise no limitations were given on time, language or age of participants. The search yielded 453 publications. Only peer-reviewed articles, studies with a longitudinal design investigating the effect of an exercise intervention and a quantitative or qualitative self-reported measure of MS fatigue were included. A screening of the 453 trials based on title and abstract resulted in 60 publications, which were closely read (Figure 1). The exercise interventions were categorized as either endurance training (ET), resistance training (RT), combined training (CT) or as 'other' (OT) training modalities. Studies evaluating the effect of different breathing modalities ($n = 3$), relaxation techniques ($n = 1$), self-management ($n = 6$), multidisciplinary interventions ($n = 9$), and osteopathic manipulative treatment ($n = 1$) were excluded. Also, case reports ($n = 5$), studies without fatigue as an endpoint ($n = 7$), non-peer-reviewed studies ($n = 1$), trial registrations ($n = 1$) and cross-sectional studies ($n = 3$) were excluded from the final analysis. This left 23 articles describing a total of 21 different trials. All reference lists of these 23 publications were checked for further relevant publications, revealing an additional two references. One of these was written in Czech and consequently excluded (Zalisova et al.). The other was included in the group of ET studies.[9]

Results

Endurance training

Compared with the other training modalities, ET has been more frequently studied (see Table 1 for overview and details of the ET studies). Ten ET studies described

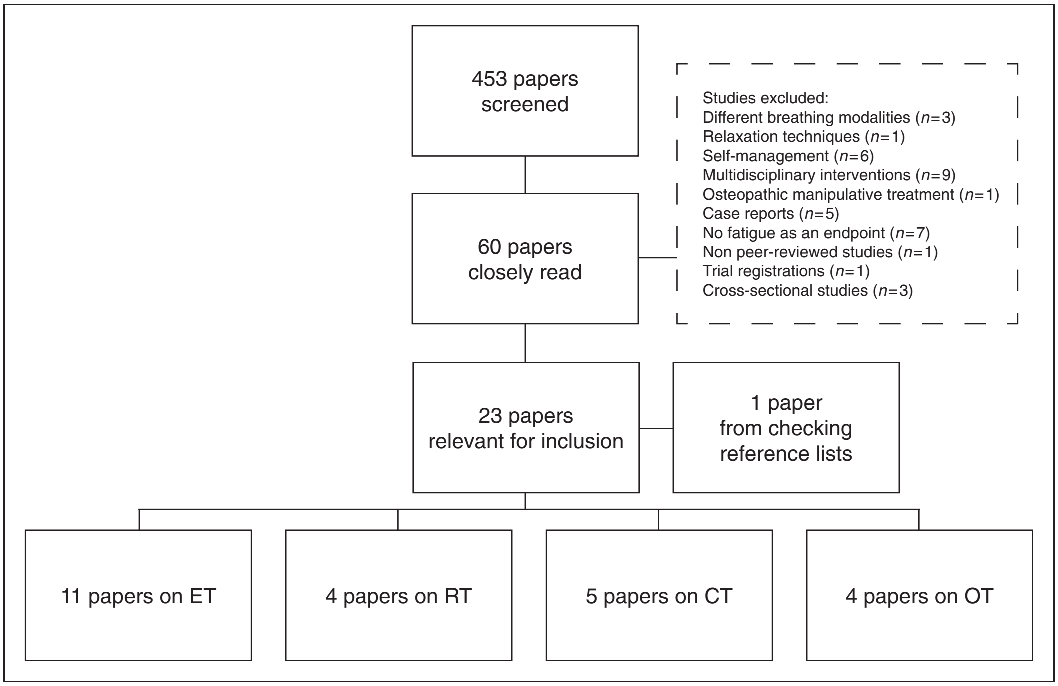

Figure 1. Flowchart showing study selection.

Table 1. Effects of endurance training on fatigue scores

Study/year	Sample size	Design	Disability (EDSS)	MS courses	Duration (weeks)/ Frequency (Days/week)	Exercise programme Intensity	Pre/Post Fatigue score	Fatigue Scale/Cut-off	Main findings
Petajan et al.[15] 1996	$n = 46$ ET:21 C:25	RCT	<6.0	NR	15/3	Arm and leg ergometry: Duration: 30 min (plus warm up and cool down 5 + 5) Intensity: 60% of VO_2 max	NR	FSS/4–5	No effect of intervention on FSS Secondary outcome.
Mostert and Kesselring[14] 2002	$n = 26$ ET: 13 C: 13 HC/HET	RCT	1–6.5	RR, CP, RP	3–4/5	Ergometer bicycling Duration: 30 min Intensity: Approx. 60% of VO_2 max	Pre/Post ET: 5.1 ± 1.8/ 4.4 ± 1.9 C: 5.2 ± 1.6/5.0 ± 1.9	FSS/4–5	No effect on FSS. Pre- vs. post intervention, within the ET group ($p = 0.09$). Primary outcome among multiple.
Kileff et al.[18] 2005	$n = 8$ ET: 8	Non-controlled	4–6	NR	12/2	Ergometer bicycling Duration: 30 min Intensity: 60–80% of HR reserve	Pre/Post ET: 50.3 ± 6.4/ 40.6 ± 8.9	FSS/(4–5) × 9 = 36–45	A trend toward an effect on fatigue. Pre- vs. post intervention, within the ET group ($p = 0.058$). Secondary outcome
Rasova et al.[17] 2006	$n = 112$ ET: 36 PT: 24 ET + PT: 19 C: 16	CT	≤6.5	NR	8/2	Ergometer bicycling Duration: 2–30 min Intensity: 60% of VO_2-max during a 6–MWT	Pre/Post ET: 36.2/32.2 PT: 42.5/34.3 ET + PT: 42.3/38.7 C: 27.0/30.9	MFIS/38	All intervention groups improved to the same extent on fatigue (MFIS pre vs. post: PT: $p < 0.0016$, ET and ET + PT: $p < 0.05$). Primary outcome
Rampello et al.[16] 2007	$n = 19$ ET:11 completed the crossover study	RCCS	≤ 6.0	NR	ET: 8/3 C: 8/3	Ergometer bicycling Duration: 30 min Intensity: 60–80% of baseline max work rate (WATT) C: 60 min of respiratory and stretching exercises	Pre/Post ET: 36(3–57)/ 29(4–56) C: 30(6–52)/ 26(3–67)	MFIS/38	No effect on fatigue of the intervention. Secondary outcome
Van den Berg et al.[11] 2006	$n = 19$ ET: 8 Delayed group: 8	RCOT, blinded.	Able to walk 10 m with aid in 60 sec	NR	4/3	Treadmill walking Duration: max 30 min. with max 3 rest periods Intensity: 55–85 of age-predicted max HR	Pre/Diff post ET: 30.6(9.2)/ −4.5(7.7) Delayed group: 32.1(9.1)/−4.4(7.8)	FSS/(4–5) × 9 = 36–45	No effect on fatigue of the intervention. Secondary outcome

(continued)

Table 1. Continued

Study/year	Sample size	Design	Disability (EDSS)	MS courses	Duration (weeks)/ Frequency (Days/week)	Exercise programme Intensity	Pre/Post Fatigue score	Fatigue Scale/Cut-off	Main findings
Newman et al.[10] 2007	$n = 19$ ET: 16	Non-controlled	NR Able to Walk 10 m with aid in 60 s	NR	4/3	Treadmill walking Duration: max 30 min. with max 3 rest periods Intensity: 55–85 of age predicted max HR	Pre/Post ET: 30(22–37)/ 27.5(12–32)	FSS/(4–5) × 9 = 36–45	No effect on fatigue ($p = 0.18$) Secondary outcome
Geddes et al.[13] 2009	$n = 15$ ET: 8 C: 4	RCT	NR	NR	12/3	Home walking programme Week 1–2: 15 min within training HR interval. Week 2–12: 20–30 min within training HR interval. Intensity: Training HR interval being 60–80% of HR reserve with HRmax determined during 6MWT	Diff pre vs. post ET: −0.24(0.72) C:−0.17(0.49)	FSS/4–5	No effect on fatigue ($p = 0.61$) Secondary outcome
Cakt et al.[12] 2010	$n = 45$ ET: 14 Active C: 10 C: 9	RCT	≤6.0	RR, SP	8/2	ET: Ergometer bicycling with increasing load. 15 sets of 2 min. of pedalling separated by 2 min of low intensity bicycling (30–40W) or 2 min of rest. And walking & stretches plus 20–25 min of balance exercise. Intensity: Initially 40% of tolerated max. workload Active control: As ET but home based and without bicycling	Pre/Post ET: 39.8 ± 9.5/ 30.2 ± 15.5 Active C: 50.0 ± 69.9/ 50.2 ± 11.0 C: 44.2 ± 2.8/ 39.0 ± 22.8	FSS/(4–5) × 9 = 36–45	Significant effect of ET on fatigue compared with Active C ($p < 0.05$) and C ($p < 0.05$). Significant correlation between 10 m walk test and FSS score ($r = 0.611$, $p = 0.003$) Primary outcome
Oken et al.[19] 2004	$n = 69$ ET: 15 YT: 22 C: 20	RCT	<6	NR	26/1 Encouraged to exercise at home	Ergometer bicycling and periodically Swiss ball training. Duration: Until fatigue or until reaching personal goals.	Pre/Post on general fatigue ET: 13.2 ± 4.0/ 12.1 ± 2.8 YT: 14.7 ± 3.3/ 13.0 ± 2.9	MFI	Significant effect of ET ($p < 0.01$) and YT ($p < 0.01$) but no difference between groups.

(continued)

Table 1. Continued

Study/year	Sample size	Design	Disability (EDSS)	MS courses	Duration (weeks)/ Frequency (Days/week)	Exercise programme Intensity	Pre/Post Fatigue score	Fatigue Scale/Cut-off	Main findings
						Intensity: Reported as light to moderate	C: 15.1 ± 3.4/ 14.9 ± 3.		Secondary outcome
Schulz et al.[9] 2004	$n = 39$ ET: 23 C: 16	RCT	<5.0	RR, SP, PP	8/2	Ergometer bicycling 30 min interval training with max intensity of 75% of max watts taken from a graded ergometer test.	Pre/Post ET: 23.0 ± 15.4/ 21.1 ± 15.0 C: 37.0 ± 15.7/ 30.3 ± 13.3	MFIS/38	No effect on fatigue ($p = 0.33$) Secondary outcome

C, Control; CP, Chronic Progressive; CT, Controlled Trial; EDSS, Expanded Disability Status Scale; ET, Endurance Training; FSS, Fatigue Severity Scale; HC, Healthy Control; HET, Healthy Endurance Training; HR, Heart Rate; MFI, Multidimensional Fatigue Inventory; MFIS, Modified Fatigue Impact Scale; NR, Not Reported; PP, Primary Progressive; PT, Physiotherapy; RCOT, Randomized Crossover Trail; RCT, Randomized Controlled Trial; RP, Relapsing Progressive; RR, Relapsing Remitting; SP, Secondary Progressive; VO_2-max, Maximal Oxygen Consumption; YT, Yoga training.

in 11 papers were retrieved. Newman et al. and Van den Berg et al. both published an article on the same study.[10,11] Seven of the studies were randomized controlled trials (RCTs)[9,11–16] and one study consecutively allocated patients into one group or the other.[17] Two studies lacked a control group.[10,18] In one study the exercise intervention was entirely home-based.[13] The other studies provided supervised training, and two studies applied a mixed programme containing both home-based and supervised training.[12,19] In general, the exercise intervention consisted of only individually prescribed ET, but in one study[12] some balance training was added to the intervention, and in another study both the active and the control group took part in a basic inpatient rehabilitation programme.[14]

The first ET study investigating the effect on MS fatigue was published by Petajan et al. in 1996 (15 weeks, 3 days/week, arm–leg ergometry).[15] Fatigue was measured with the FSS, which is a nine-item scale with scores ranging from 1–7. The cut-off score for fatigue has been reported as between four and five (mean value of the nine items).[20] In the Petajan et al. study, the baseline sum score in the exercise group was 48.7 ± 2.0 (mean item score ~5.4), indicating a fatigued study population. After the exercise intervention there was a significant improvement on physical fitness (Maximal Oxygen Consumption (VO_2-max)) in the exercise group compared with the non-exercise group, an effect on the FSS score was also seen after 10 weeks but not at the final assessment after 15 weeks. Mostert and Kesselring studied the effect of ergometer bicycling at the aerobic threshold, but no effect could be demonstrated on the aerobic threshold and only a tendency towards a reduction was observed on the FSS score (4 weeks, 5 days/week).[14] In a pilot study by Kileff and Ashburn, six out of eight participants completed the study (12 weeks, 2 days/week, bicycling) and improved on the six-minute walk test.[18] Even though the FSS sum score fell from 50 ± 6 to 41 ± 9, the improvement was not significant. Rasova et al. assigned 95 patients with MS into three training groups (ET, ET and physiotherapy, physiotherapy) and one non-intervention control group (8 weeks, 2 days/week, bicycling).[17] The VO_2-max did not improve but cycling performance (watt/kg) increased significantly compared with the control group, and fatigue assessed with the Modified Fatigue Impact Scale (MFIS) decreased. The study contained many endpoints but was not corrected for multiple comparisons.

Rampello et al. conducted a controlled randomized crossover study (8 weeks, 3 days/week, bicycling).[16] Baseline fatigue score (MFIS) was below the cut-off score of this scale. Several fitness related parameters, for example, VO_2-max and maximal walking speed, improved significantly, but the MFIS score did not change significantly. Newman et al. and Van den Berg et al. investigated the effect of treadmill training.[10,11] Post intervention, the 10 m walk time improved. Also, at a higher speed of 'comfortable walking', the oxygen consumption decreased in the training group compared to the control group (4 weeks, 3 days/week). At baseline the participants were non-fatigued and the FSS score did not change after the intervention. Geddes et al. investigated the effect of a home-based walking programme (12 weeks, 3 days/week).[13] No significant improvements were reported compared with controls, either with respect to physical fitness or fatigue. The most recent study, here categorized as ET, was conducted by Cakt and colleagues.[12] Participants were divided into three groups. ET performed by group 1 was bicycling, walking, stretching and balance exercise. Group 2 trained as group 1 without bicycling and all training was home-based. Group 3 continued daily living as usual (8 weeks, 2 days/week). Among improvements in group 1 were duration of exercise, tolerated maximum workload and 10 m walk time. Also, compared with other groups, the fatigue score (FSS) decreased in group 1. Oken et al. investigated the effect of ET, yoga (YT) or no intervention on cognition, fatigue, mood and quality of life (26 weeks, 1 day/week, bicycling).[19] Measured with the Multidimensional Fatigue Inventory (MFI), the effect on general fatigue was similar in both active groups. Schulz et al. investigated the impact of ET on immune–endocrine parameters, neurotrophic factors, coordinative function and factors influencing quality of life (8 weeks, 2 days/week, bicycling).[9] Also, fatigue was assessed with MFIS. The intervention had no effect either on the total score or any subscales.

Resistance training

Three RT studies and four papers were retrieved from the literature search (see Table 2 for overview and details of the RT studies). Only the study by Dalgas et al. is an RCT.[7] The other studies compare the difference between pre and post measurements in subjects exposed to RT. The study by Dodd et al. is a qualitative analysis of the effect of progressive RT on eight patients with MS performing supervised training (10 weeks, 2 days/week).[21] Muscle strength of both arms and legs improved, and muscle endurance was improved in the leg press exercise. One participant experienced increased fatigue in the days after training, whereas the rest of the participants felt that they had reduced level of fatigue as the study progressed. The 'Florida group' published two articles on the same study, a small-scale non-controlled trial evaluating the effect of supervised RT (2 days/week, 10 weeks).[22,23] Both leg muscle strength and gait kinematics improved significantly. Fatigue (MFIS) decreased, corresponding to 24% of the baseline value. In the randomized controlled progressive RT study by Dalgas et al., exercise sessions were supervised and mostly conducted in groups (12 weeks, 2 days/week).[7] All subjects scored >4 on the FSS at baseline, indicating that participants were fatigued. Leg muscular strength and functional capacity improved significantly. Fatigue (FSS), depression score and quality of life also improved significantly, and the effect was maintained at a 12-week follow-up.

Combined training

The effect of combined ET and RT on MS fatigue has been investigated in five studies (see Table 3 for overview and details of the CT studies). The first study is a large RCT.[24] After five supervised training sessions during a three-week inpatient rehabilitation programme, patients continued with a home-based CT programme lasting from week 4 to week 26 (ET: 1 day/week, RT: 3–4 days/week). In the female participants of the exercise group, motor fatigue of knee flexion was reduced. The baseline FSS score was of 4.6 ± 1.6, and a trend toward an effect of CT on fatigue was found. Fragoso et al. conducted a non-controlled trial in a group of patients with MS attending regional MS meetings and complaining of fatigue.[25] The training protocol was adjusted to fit each subject's individual needs (20 weeks, 3 days/week). Among multiple cardio-circulatory parameters heart rate improved and Chalder's fatigue score decreased. Plow and colleagues compared the effects of a combined rehabilitation programme with a group wellness intervention (GWI) programme regarding stress, depression, energy conservation and priority setting.[26] The home-based CT program (5 days/week, 7 weeks) was supported by four physical therapy sessions every other week and telephone calls. After initial GWI sessions the GWI group performed the same home-based exercise programme as the CT group. At the end of intervention (8 weeks) no changes were found, but at follow-up both groups had improved to a similar extend on strength, heart rate and fatigue (MFI). Smith et al. assessed the effect of individualized supervised training (8 weeks, 3 days/week).[27] Five inter-related fatigue categories were identified, among which were 'listening to your body' and 'perceived control over fatigue'. Exercise up to or beyond a certain limit, 'reaching the edge', was crucial for the perception of either a positive exercise outcome or of physical deterioration and negative feelings. Positive perceived changes occurred progressively during the 8 weeks of exercise; however, participants also experienced fluctuating outcomes from one session

Table 2. Effect of resistance training on fatigue scores

Study/year	Sample size	Design	Disability (EDSS)	MS Courses	Duration (weeks)/ Frequency (Days/week)	Exercise programme. Intensity	Baseline Fatigue (Score)	Fatigue Scale/ Cut-off	Main findings
Dodd et al.[21] 2006	$n = 9$ RT: 8	Non-controlled	NR	NR	Familiarization (4 weeks) 10/2	3 machine exercises (upper- and lower extremities) All weeks: 2 sets of 10–12 reps at 10–12 RM		Qualitative study based on semi-structured in-depth interviews	1/8 reported increased fatigue. 7/8 reported decreased fatigue
Florida group White et al.[23] 2004 Gutierrez et al.[22] 2005	$n = 8$	Non-controlled	2.5–5.5	RR	8/2	5 machine exercises (lower extremities) *Week number 1:* 1 set of 6–10 reps; *2–8:* 1 set of 10–15 reps. *Intensity at week number 1:* 50% MVC; *2:* 60% MVC; *3–8:* 70% MVC. When 15 reps were performed: + 2-5% MVC.	Pre/Post $32 \pm 18/25.8 \pm 17$	MFIS/38	Significant effect of RT within the group ($p < 0.05$) Secondary outcome
Dalgas et al.[7] 2010	$n = 38$ RT: 15 C: 16	RCT	3.0–5.5 Pyramidal score ≥ 2	RR	12/2	5 machine exercises (lower extremities) Week number 1–2: 3 sets of 10 reps at 15 RM; 3–4: 3 sets of 12 reps at 12 RM; 5–6: 4 sets of 12 reps at 12 RM; 7–8: 4 sets of 10 reps at 10 RM; 9–10: 4 sets of 8 reps at 8 RM; 11–12: 3 sets of 8 reps at 8 RM.	Pre/Post RT: FSS 5.8(5.4–6.1)/5.2 (4.4–6.0); MFI 12.9 (10.9–14.9)/12.1(10.2–13.8) C: FSS 5.5 (5.0–6.0)/5.6 (4.9–6.3); MFI 11.6 (9.7–13.4)/13.7 (11.7–15.7)	FSS/4–5 MFI–20	Significant effect of RT compared to C (FSS $p < 0.04$; MFI $p < 0.004$) Secondary outcome

C, Control; EDSS, Expanded Disability Status Scale; FSS, Fatigue Severity Scale; MFI, Multidimensional Fatigue Inventory; MFIS, Modified Fatigue Impact Scale; MVC, Maximal Voluntary Contraction; NR, Not Reported; RCT, Randomized Controlled Trial; RR, Relapsing Remitting; Reps, Repetitions; RT, Resistance Training; RM, Repetition Maximum.

Table 3. Effect of combined training on fatigue scores

Study/year	Sample size	Design	Disability (EDSS)	MS courses	Duration (weeks)/ Frequency (Days/week)	Exercise programme Intensity	Baseline Fatigue (Score)	Fatigue Scale/Cut off	Main findings
Surakka et al.[24] 2004	$n=95$ CT: 44 C: 44	RCT	1-5.5	All	26/ Frequency: Week 1–3: RT 5, ET 5 Week 4–26: RT 3–4, ET: 1	Week 1–3: Inpatient rehab. Programme Week 4–26: RT: Circuit training, 10 exercises for whole body, 2 sets of 10–15 reps. ET: Aquatic training or preferred mode of ET. Intensity: Stiffer elastic band at week 15	Pre CT: 4.6 ± 1.6 woman/4.6 ± 1.6 men C: 4.7 ± 1.2 woman/4.5 ± 1.1 men (SEM not SD)	FSS/4–5	No effect of the CT intervention on fatigue. Secondary outcome
Fragoso et al.[25] 2008	$n=10$ CT: 9	Non-Controlled	≤6.0	RR, SP	20/3	Week 1–4: 60 min of progressive stretching. Week 5–14: 15 min progressive stretching and 30 min resistance training with lightweights. Week 15–20: 30 min stretching, 30 min resistance training and 30 min walking/running	Pre/Post 46 ± 6.3/39.4 ± 3.4	Chalder's Fatigue Scale	Significant effect of CT ($p=0.01$) Primary outcome
Plow et al.[26] 2009	$n=50$ CT: 22 C: 20	RCT	NR	NR	CT: IPR: 8/ every other week + HE 7/5 C: GWI: 7/ 1 + HE 6/5	CT: 4 sessions of IPR and HE. C: GWI of 120 min each week HE: 45 minutes of ergometer bicycling (3/week) and stretching & balance training 2/week	Average diff of pre- vs. post- scores IPR: 0.66 GWI: 0.14 Diff between groups: 0.52	MFI	No effect of the CT intervention on fatigue. Primary outcome among several measures.
Smith et al.[27] 2009	$n=10$ CT: 10	Non-controlled	NR Able to walk a short distance independently	NR	8/3	One-hour IPT: Endurance training, strengthening, balance exercises and stretching.		Qualitative study using Interpretive Description methodology	CT is related to both positive and negative changes in fatigue. Important categories are: 'listening to your body' and 'perceived control over fatigue' and 'reaching the edge'. Primary outcome

(continued)

Table 3. Continued

Study/year	Sample size	Design	Disability (EDSS)	MS courses	Duration (weeks)/ Frequency (Days/week)	Exercise programme Intensity	Baseline Fatigue (Score)	Fatigue Scale/Cut off	Main findings
McCullagh et al.[28] 2008	$n = 30$ CT: 12 C: 12	RCT		RR SP	12/2	Four modalities of 10 minutes (endurance training, strengthening and balance activities. 2 × 5 min of warm up and cool down). Intensity: On Borgs scale for Rating of Perceived Exertion intensity was encouraged to be "fairly light" to "somewhat hard"	Pre/Diff Pre-Post CT: 26 (17; 40.5)/-13(-20.5; -3) C: 26.5 (21.5; 33.5)/1(-4;+4.5) mean (interquartile range)	MFIS/38	Significant effect of CT between groups ($p = 0.02$) Primary outcome

C, Control; CT, Combined Training; EDSS, Expanded Disability Status Scale; ET, Endurance Training; FSS, Fatigue Severity Scale; HE, home exercises; GWI, Group Wellness Intervention; IPT, Individualized Physiotherapy; IPR, Individualized Physical Rehabilitation; MFI, Multidimensional Fatigue Inventory; MFIS, Modified Fatigue Impact Scale; NR, Not Reported; RCT, Randomized Controlled Trial; RR, Relapsing Remitting; RT, Resistance Training; SP, Secondary Progressive.

to another. McCullagh et al. conducted a randomized controlled pilot study comprising supervised individualized training and a home-based exercise programme (12 weeks, 2 days/week).[28] Compared with the control group, the CT group improved on both the MFIS and Functional Assessment of Multiple Sclerosis (FAMS) after 12 weeks and at follow-up after 6 months.

Other types of exercise

Two studies investigating the effect of aquatic therapy on MS fatigue were found (see Table 4 for overview and details of the OT studies). The rationale justifying aquatic therapy is that the water will prevent the body temperature from increasing and thereby enable thermosensitive individuals to complete or to prolong their training sessions. Broach et al. focused on fatigue and motor parameters, for example walking on stairs, rotations on a bicycle and on an upper-body ergometer (8 weeks, 3 days/week).[29] The design was a single-subject, multiple-probe design. This design is similar to a multiple baseline design in that it is introduced to one participant at a time. Results suggested an improvement of motor performance and a decrease of physical fatigue, whereas an effect on mental fatigue could not be demonstrated. Roehrs and Karst conducted a large-scale pilot study investigating the effect of aquatic exercise and identifying barriers to participation in exercise programmes (12 weeks, 2 days/week).[30] Of 31 subjects, 19 participated in at least 25% of the planned sessions and fatigue decreased (MFIS). Also, quality of life improved, with better social functioning after the intervention.

Discussion

Few existing studies have evaluated MS fatigue as the primary outcome measure, and studies evaluating the effect of exercise therapy on MS fatigue show heterogeneous results. However, the overall interpretation is that exercise therapy has the potential to reduce MS fatigue. The influence of ET on MS fatigue has been evaluated in 10 studies, and some demonstrated a substantial effect. In the group of ET studies, three address fatigue as the primary outcome measure. Also, designs show great heterogeneity regarding sample size, intervention period, exercise intensity and frequency, and session duration. Studies showing an effect of ET are generally characterized by applying large sample sizes and by applying a study population who were fatigued at study start. Three small studies have evaluated the effect of RT on MS fatigue, including only one RCT. These show promising treatment effects by consistently reporting improvement of fatigue after RT, but here fatigue is a secondary outcome measure in all studies. Five studies evaluated the

Table 4. Effect of other training modalities on fatigue scores

Study/ year	Sample size	Design	Disability (EDSS)	MS Courses	Duration (weeks)/ Frequency (Days/week)	Exercise programme. Intensity	Baseline Fatigue (Score/Cut-off)	Fatigue Scale	Main findings
Broach and Dattilo[29] 2001	$n=4$ OT: 4	Single subject. multiple-probe design	NR	RR	8/3	Four phase Aquatic therapy: 10 min walking warm-up, 10 min of step exercises, 18 min of upper body exercises, and 7 min of lower body exercises. Intensity: NR	NR	Chalder's fatigue scale	Visual analysis of data suggests that all participants improved on physical fatigue. No effect on mental fatigue could be established. Primary endpoint
Roehrs and Karst[30] 2004	$n=31$ OT: 18	Non-controlled	1.5-8	PP, SP	12/2	One hour individualized aquatic therapy: Warm up, stretching, endurance training, balance activities, and strengthening.	Pre/Post 48.7 ± 12.1/ 43.5 ± 15.0	MFIS/38	Significant effect of OT within the group ($p=0.035$) Primary endpoint

EDSS, Expanded Disability Status Scale; ET, Endurance Training; MFIS, Modified Fatigue Impact Scale; NR, Not Reported; OT, Other Training; PP, Primary Progressive; RR, Relapsing Remitting; SP, Secondary Progressive.

effect of CT on MS fatigue, including three RCTs. One RCT shows no effect on MS fatigue, one RCT shows an effect, and the largest and longest RCT shows a trend towards an effect. Also, other training modalities than ET, RT and CT, such as aquatic therapy, may positively impact MS fatigue.

Fatigued versus non-fatigued study populations

Regarding the diverse results of studies, the importance of study populations must be considered. The majority of studies have investigated non-fatigued groups of patients with MS, and it can be questioned whether it is relevant to evaluate the dynamics of a non-pathological degree of fatigue; thus the level of evidence from this group of studies may be limited.[9–11,16,17,22,23,28] Also, this may explain why most of these studies[10,11,15,16,22,23] do not report an effect of exercise therapy on MS fatigue, as opposed to studies on groups who were fatigued at baseline (fatigue scores close to or above the cut-off value of the applied fatigue scale).[7,12,17,18,30] In only the studies by Mostert and Kesselring[14] and by Surakka et al.[24] were participants fatigued MS patients but the exercise interventions showed no effect. The short duration of the exercise period in the study by Mostert and Kesselring[14] may have limited this study. In the study by Surakka et al.,[24] a trend toward a training effect was actually observed ($p=0.07$). Also, it should be noted that the study by Rasova et al.[17] included a non-fatigued control group in contrast to the intervention groups, compromising the reliability of their positive results.

Effect of exercise modality

Our review shows that ET, RT, CT and other types of exercise such as aquatic activities have the potential to reduce MS fatigue. So far only a few studies have compared the effects of different exercise modalities, making conclusions regarding the optimal exercise modality difficult. Neither Oken et al.[19] nor Rasova et al.[17] found differences between the interventions when comparing the effects of ET and yoga and ET and physiotherapy on MS fatigue, respectively. RT has consistently shown positive effects on MS fatigue, leading to the speculation that RT might be more efficient than ET. However, no studies have compared these two exercise modalities.

Duration, frequency and intensity

It is not possible to draw solid conclusions on optimal exercise duration, frequency and intensity. Most studies evaluating ET have applied an exercise frequency of 2–3 days a week, exercise intensities in the range of

60–80% of maximal heart rate and an exercise duration of approximately 30min a day, with intervention periods ranging from 3–26 weeks.[9–13,15–19] Interestingly, the study by Oken et al.[19] showed an effect on fatigue, whereas the study by Mostert and Kesselring[14] did not. Mostert and Kesselring evaluated the effects of a high-frequency training programme with short duration (5 days/week, 3–4 weeks),[14] whereas Oken et al., in contrast, evaluated a low-frequency programme of long duration (1 day/week, 6 months).[19] In both studies, ergometer bicycling at a light to moderate intensity was applied. Cakt et al. reported reduced fatigue after a low-frequency training programme (2 days/week, 8 weeks, bicycle ergometry and a home-based training programme).[12] However, Cakt et al. applied a more intense interval protocol. Taken together, this indicates that longer low-frequency ET intervention periods and relatively shorter but more intense low-frequency protocols are superior to high-frequency, short-duration protocols.

The existing RT studies have all applied an exercise frequency of 2 days a week during a total of 8–12 weeks, with exercises mainly aiming at the lower extremities. All studies show reduced fatigue, suggesting that improvements can be obtained after an 8-week exercise period. The research conducted on combined exercise protocols demonstrates varied degrees of effects, but it seems that training comprising ET, RT and balance exercises or stretching, divided in three equal proportions, performed 2–3 times a week for 40–60 min, has a beneficial effect on MS fatigue.

Effect of scale selection

The most common scale used to monitor the effect of exercise therapy on MS fatigue is the FSS scale.[7,10–15,18,24] Recently both the FSS and the MFIS have undergone Rasch analyses and in general the dimensions of the scales are questioned. The FSS was found to measure social consequences of fatigue to a greater extent than the intensity of fatigue itself (subjective fatigue), and the MFIS was found suitable for measuring the dimensions cognitive and physical fatigue only, but not general fatigue.[31,32] Few scales have well-defined cut-off values regarding MS fatigue. Penner et al. have introduced the MS-specific ‘Fatigue Scale for Motor and Cognitive Functions’ (FSMC) which has well established cut-off values, and the scale has been translated into multiple languages.[33] The newer MS fatigue scales may provide more detailed information in future studies.

Effects of socialization

Some of the positive studies in the present review involved a social component, for example, supervised training, group exercise and contact with other participants. Psychosocial factors may affect patients’ interpretation of symptoms and thereby break detrimental cognitive–behavioural habits that aggravate fatigue. The social interaction related to training in the present studies may have influenced the perception of fatigue. However, social interaction is often a natural part of exercise therapy, or at least easily can be.[34,35]

Motor mechanisms related to MS fatigue

MS fatigue is probably a consequence of MS-specific neuropathological alterations, and may also be related to physical and cognitive impairments. A physiological explanation for muscle fatigue is dysfunction of the motor system or its neural activation that arises due to altered properties within the muscle, or because the central nervous system fails to drive the motor neurons sufficiently.[36] Patients with MS have reduced muscle performance, and their muscles show characteristics of disuse such as reduced muscle fibre size and a shift in the proportion of fibre types from type 1 fibres towards a greater proportion of type IIa and IIax fibres, or an increase in the proportion of hybrid fibres expressing myosin heavy chain I/IIa/IIx.[37–39] However, in accordance with the pathophysiological mechanisms of MS, excessive physiological motor fatigue is mainly central in origin, rather than a consequence of intramuscular changes. Suboptimal central neuronal drive leads to incomplete activation of muscles, and MS fatigue is related to decreased central motor activation.[40,41] However, a relationship between peripheral muscle fatigue and suboptimal output from the motor cortex has also been established.[42] When a muscle at the end of a fatiguing contraction is prevented from recovery by holding the muscle ischaemic, fatigue-sensitive muscle afferents act upstream of the motor cortex and inhibit the voluntary descending drive. Efferent high-frequency fatigue is thereby prevented, but the maximal muscle strength is also reduced.[43,44] In healthy subjects RT improves central motor activation,[45] in MS patients RT enhances the efferent motor drive,[46] and in MS RT seems to reduce MS fatigue. The perception of worsened fatigue after overtraining may occur as a consequence of afferent inhibition from strained muscles.

Another plausible mechanism behind the effect of exercise on MS fatigue is a training-induced up-regulation of neuroendocrine growth factor production, which increases neuronal plasticity and thereby possibly improves compensatory cortical activation.[47,48] Also, an exercise-induced up-regulation of anti-inflammatory cytokines may have a beneficial effect on MS fatigue.[9,49,50]

A multidimensional approach against MS fatigue

Predominant secondary causes of MS fatigue are depression, stress, low self-efficacy, poor sleep and pain, which may be modified. Sleep disturbances are the most disturbing.[51,52] In a recent expert review by Krupp et al., a multidisciplinary treatment approach is recommended, including cognitive–behavioural therapy, exercise therapy and substantial effort to reduce secondary fatigue-inducing factors. Based on the present review, exercise therapy seems to have an effect on MS fatigue and we suggest that exercise therapy should comprise a substantial part of the multidimensional approach.[53]

Conclusions

Exercise therapy has the potential to induce a positive effect in MS fatigue, but findings are heterogeneous probably because many studies have used non-fatigued study populations. Furthermore, only a few studies have evaluated MS fatigue as the primary outcome measure, emphasizing the need for future studies within this field. Future studies should be designed as RCTs with fatigue as the primary endpoint. Fatigue scales should be multidimensional and have well-established cut-off values. Secondary fatigue-inducing parameters are of interest, as is the influence of MS subtype and level of disability.

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