Effectiveness of Fatigue Management Interventions in Reducing Severity and Impact of Fatigue in People with Progressive Multiple Sclerosis

A Systematic Review

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CME/CNE Information

Activity Available Online:
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Target Audience:
The target audience for this activity is physicians, physician assistants, nursing professionals, and other health care providers involved in the management of patients with multiple sclerosis (MS).

Learning Objectives:
1) Identify different methods of managing fatigue in people with progressive MS and the effectiveness of these interventions.
2) Analyze the limitations of the current available evidence.

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Background: **Rehabilitation interventions are recommended to manage multiple sclerosis (MS)–related fatigue. However, existing research has largely been generalized to those with relapsing-remitting MS, making it difficult to determine the effectiveness of these interventions in people with progressive MS. Therefore, this study aimed to systematically review the evidence related to the effectiveness of fatigue management interventions in reducing the severity and impact of fatigue in people with progressive MS.**

Methods: **Six electronic databases (CINAHL, Cochrane Library, MEDLINE, PEDro, ProQuest, and Web of Science Core Collections) were searched for relevant articles up until November 2017. Randomized controlled trials and quasi-experimental studies that examined the effects of exercise, behavioral interventions, and rehabilitation on fatigue in people with progressive MS using self-reported fatigue outcome measures were included in this review.**

Results: **Eight exercise, two rehabilitation, and two behavioral interventions were investigated in the 13 articles included in this review. Heterogeneous effects were reported between studies, with only two exercise, one behavioral, and two rehabilitation interventions recording significant improvements in postintervention fatigue severity or impact. However, most studies were underpowered, only two used fatigue as the primary outcome, and only one specifically recruited participants with predefined levels of fatigue.**

Conclusions: **Evidence from this review is inconclusive regarding the effectiveness of nonpharmacologic interventions in reducing the severity and impact of fatigue in progressive MS populations. Adequately powered randomized controlled trials are required to evaluate fatigue management interventions in people with progressive MS experiencing high levels of fatigue and using fatigue as the primary outcome.** ***Int J MS Care.*** **2019;21:34-46.**

Fatigue is a common symptom of multiple sclerosis (MS), reported in more than 70% of the population.[1-3] Fatigue related to MS is often perceived as the most debilitating symptom, which significantly affects activities of daily living, social participation, and quality of life[4,5] and is associated with changes in employment.[6] Fatigue is a highly complex and multifactorial symptom that may be defined as "a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities."[7(p2)] Subjectively, this may be described as exhaustion, a lack of energy, or overwhelming tiredness that is pervasive and can occur at rest.[8]

Although fatigue can be experienced throughout the course of MS, it has a higher prevalence in people with progressive forms of the disease.[1,9,10] Primary pathologic disease processes involving structural and functional central nervous system changes, and secondary factors independent of MS pathology, are associated with fatigue pathogenesis.[11-13] However, because the pathophysiologic mechanisms underlying fatigue in MS are not well understood,[11-13] current treatment strategies are focused on symptom management through nonpharmacologic interventions.[14]

Rehabilitation interventions are recommended to manage MS-related fatigue,[14] and several studies have demonstrated that interventions such as exercise, energy conservation management, and cognitive behavioral therapy have moderate, positive short-term effects on fatigue outcomes.[15-18] However, results have largely been generalized to those with relapsing-remitting MS (RRMS), with few studies making a distinction between RRMS and progressive MS populations. Therefore, in line with the International Progressive MS Alliance research priorities,[19] there is a need to determine the effectiveness of fatigue management interventions in people with progressive MS owing to the high prevalence and impact of fatigue in this population. Hence, the aim of this work was to systematically review the evidence related to the effectiveness of fatigue management interventions in reducing the severity and impact of fatigue in people with progressive MS. To achieve this aim, the following objectives were met: 1) to summarize the details of fatigue management interventions for people with progressive MS, 2) to critically evaluate the effectiveness of fatigue management interventions

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in reducing the severity and impact of fatigue in people with progressive MS, and 3) to identify limitations of the current evidence to inform the direction of future study.

Methods

A review protocol was developed and registered with the PROSPERO database in December 2017 (number: CRD42017082203).

Search Strategy

Searches of the following databases were conducted from inception to November 2017: CINAHL (via EBSCOhost), Cochrane Library, MEDLINE (via Ovid), PEDro, ProQuest (Health & Medical Collection, Nursing & Allied Health Database, and PsycINFO), and Web of Science Core Collections. Search strategies included a combination of keywords and subject headings related to MS, exercise, behavioral therapy, rehabilitation, and fatigue and were adapted for use in each different database (Table S1, which is published in the online version of this article at ijmsc.org). Reference lists of relevant review articles were also hand searched to identify any additional articles. After each database was searched, results were exported to Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) and duplicates were removed before screening. The primary reviewer (S.R.) initially screened all articles by title and then by abstract against the inclusion and exclusion criteria. Subsequently, two reviewers (S.R. and L.P.) independently screened full texts of the remaining articles for eligibility. Disagreements were resolved through consensus in consultation with a third reviewer (F.M.) if required.

Inclusion and Exclusion Criteria

To be included in this review studies had to have 1) recruited adults with a definite diagnosis of MS and a progressive form of the disease (secondary or primary progressive), 2) evaluated nonpharmacologic interventions in accordance with the definitions provided in Table 1, 3) used a self -reported measure of fatigue impact or severity as either a primary or secondary outcome (including subscales of questionnaires), 4) used a randomized controlled trial (RCT) or quasi-experimental design, and 5) been published in English. Studies that included a combination of types of MS were included only when specific results for those with progressive MS could be identified. Nonhuman studies, pharmacologic studies, and conference proceedings and abstracts were excluded from this review.

Table 1. Definitions of included interventions

Intervention	Definition
Exercise	Exercise was defined as "planned, structured and repetitive bodily movement carried out to improve or maintain one or more components of physical fitness"; this definition included conventional aerobic and resistance-based exercise, task-orientated exercise, and alternative exercise methods.[20]
Behavioral	For behavioral interventions, studies must state or describe a behavioral therapy intervention that aimed to facilitate behavioral or attitudinal changes. Common behavioral interventions are cognitive behavioral therapy, mindfulness, or interventions aimed at modifying behavior specifically in relation to energy conservation or symptom self-management.[14]
Rehabilitation	Rehabilitation interventions included treatment strategies that aimed to maintain or improve current level of function, or prevent loss of function, and were delivered in a hospital (inpatient or outpatient) or community-based setting by a multidisciplinary team of relevant health care professionals.[21] Exercise or behavioral interventions were classified as rehabilitation interventions if additional treatment components were delivered alongside these interventions.

Data Extraction

Data extraction was completed independently by one reviewer (S.R.) using a standardized data extraction form. The data extraction form was developed based on CONSORT (Consolidated Standards of Reporting Trials) and TIDieR (Template for Intervention Description and Replication) guidelines.[22,23]

Quality Assessment

Quality of evidence was assessed using the Downs and Black checklist, a 32-point scale developed for quality assessment of RCTs and non-RCTs.[24,25] An initial quality assessment was conducted in which each of the three reviewers (S.R., F.M., and L.P.) independently scored an article to ensure consistency in assessment between reviewers. After this quality assessment, question 27 of the checklist was modified such that an article was assigned 1 point for including a sample size calculation and zero if the article did not, resulting in a total possible score of 28. This modification was implemented in keeping with two systematic reviews of exercise inter-

ventions in MS.[26,27] Quality assessment was completed independently by two reviewers. When discrepancies arose, agreement was reached through consensus in consultation with a third reviewer.

Data Synthesis

Owing to the inclusion of quasi-experimental studies and the heterogeneity in study design, it was not feasible to conduct a meta-analysis; therefore, results were generated through narrative synthesis. Preliminary synthesis involved a descriptive summary of key information extracted from all articles. Individual study estimates of treatment effects were presented under each mode of intervention and explored within and between studies considering moderator variables to explain differences in results. Where available, results for the relevant fatigue outcome measures were compared with minimal clinically important difference (MCID).

Results

Search Results

Through searching the selected electronic databases, 560 articles were identified, and an additional four articles were added from reference lists of relevant studies (Figure 1). After removing duplicates, 463 articles remained for title and abstract screening, of which 308 were excluded by title and 97 by abstract. The remaining 58 articles were included for full-text screening. After screening full texts, 45 articles were excluded because the results of those with progressive MS were not identifiable in 41 studies (either MS type was not reported or results for those with progressive MS were not presented separately), three studies did not include participants with progressive MS, and one study did not include a fatigue outcome measure. Two articles described the same study but reported different outcome measures[29,30]; therefore, 13 articles[29-41] from 12 studies were included (Table 2).

Study Design

Of the included articles, six were RCTs[31,32,36,37,39,41] and seven were quasi-experimental studies (pretest/posttest design [n = 4],[34,35,38,40] non-RCT design [n = 2],[29,30] or nonrandomized crossover trial design [n = 1][33]). All but one RCT included two trial arms (control and intervention); the study by Briken et al[36] involved three intervention conditions in addition to the control group. The length of the intervention period ranged from 4 to 52 weeks; however, most studies delivered interventions for 12 weeks or less (n = 11), with only one rehabilitation intervention lasting 52 weeks.[29,30] Four articles reported follow-up outcome assessments conducted 4,[32,39] 6,[41] or 8[33] weeks after the intervention.

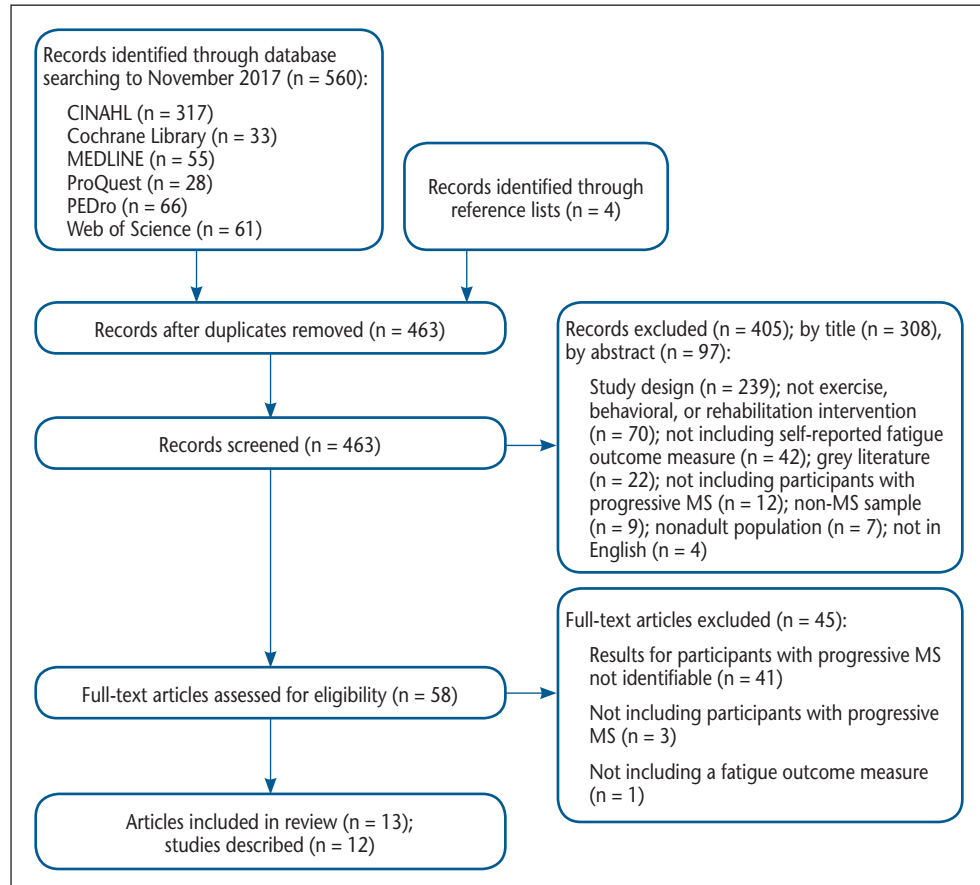

***Figure 1.* PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram[28]**

MS, multiple sclerosis.

Table 2. Characteristics of included articles (page 1 of 3)

Study; design; intervention	Sample details	Intervention type, delivery mode, duration, frequency	Fatigue outcome measure; time points	Main findings[a]
Di Fabio et al,[29] 1997; quasi-experimental (non-RCT); rehabilitation	N = 44 (25 F/6 M)[b]; all progressive MS, SPMS: NR, PPMS: NR; EDSS, 5-8; dropout, 13 (30%)	Outpatient rehabilitation program (n = 19): delivered in MS treatment center by PTs, OTs, and supportive services; Waitlist control (n = 25); 52 wk, 1 d/wk, 5 h	SF-36 vitality subscale (secondary); 0, 52 wk	SF-36 (vitality): Within group (effect size): I = 0.3; C = –0.39
Di Fabio et al,[30] 1998; quasi-experimental (non-RCT); rehabilitation	N = 46 (34 F/12 M); all progressive MS, SPMS: NR, PPMS: NR; EDSS, 5-8; dropout, 13 (28%)	Outpatient rehabilitation program (n = 20): delivered in MS treatment center by PTs, OTs, and supportive services; Waitlist control (n = 26); 52 wk, 1 d/wk, 5 h	MS-Related Symptom Checklist fatigue subscale (primary); 0, 52 wk	MS-Related Symptom Checklist fatigue: Baseline[c]: I = 2.9 ± 0.32, C = 3.2 ± 0.25; Within-group (effect size): I = 0.46; C = –0.20; Between groups: $P = .004$
Patti et al,[31] 2003; RCT; rehabilitation	N = 111 (64 F/47 M); all progressive MS, SPMS: NR, PPMS: NR; EDSS, 4-8; dropout, 13 (12%)	Outpatient rehabilitation program (n = 58): rehabilitation included physiotherapy, OT, speech therapy, supportive treatments, group physiotherapy; 6 wk, 6 d/wk, followed by 6 wk of home exercise; Home exercise control (n = 53): 12 wk of home exercise program	FIS (secondary); 0, 6, 12 wk	FIS: Baseline: I = 116.8 ± 40.9, C = 127 ± 36; 12 wk (MD): I = –18.8 ± 14.3, $P < .001$, C = 0.6 ± 0.9, $P > .05$; Between groups: $P < .001$
Klefbeck and Nedjad,[32] 2003; RCT; exercise other	N = 16 (6 F/9 M)[b]; all progressive MS, SPMS: NR, PPMS: NR; EDSS , 6.5-9.5; dropout, 1 (6%)	IMT (n = 8): 10 wk, 10 min of training 2× every other day consisting of 3 sets of 10 loaded inspirations using threshold IMT device with 1-min rest between sets; Control (n = 8): usual physiotherapy care	FSS (secondary); 0, 10, 14 wk	FSS: Baseline: I = 5 ± 1.3, C = 4.5 ± 1.3; Between groups (10 wk): $P > .05$
Vanage et al,[33] 2003; quasi-experimental (nonrandomized crossover trial); behavioral	N = 37 (29 F/8 M); all progressive MS, SPMS: NR, PPMS: NR; EDSS, ≥5; dropout, 9 (24%)	Group-based (3-8 participants per group) energy conservation course modified for those with increased disability, delivered by OTs in rehabilitation center; Group A: intervention followed by control (n = 21), Group B: control followed by intervention (n = 16); Control: chaplaincy-led support group; 8 wk, 1 session/wk, 60 min	FIS (primary); Preintervention, postintervention, 8-wk follow-up	FIS (total): Pre/postintervention: MD = 15.7 ± 25, effect size = 0.89, $P < .01$; Postintervention, 8-wk follow-up: MD = 2.1 ± 23.7, effect size = 0.13, $P > .05$. FIS (physical): Pre/postintervention: MD = 4.2 ± 7.9, effect size = 0.75, $P < .01$; Postintervention, 8-wk follow-up: MD: 1 ± 8.1, effect size = 0.17, $P > .05$. FIS (cognitive): Pre/postintervention: MD = 4 ± 6.8, effect size = 0.82, $P < .01$; Postintervention, 8-wk follow-up: MD = –0.4 ± 7.2, effect size = –0.08, $P > .05$. FIS (psychosocial): Pre/postintervention: MD = 7.5 ± 12.7, effect size = 0.83, $P < .01$; Postintervention, 8-wk follow-up: MD = 1 ± 13.3, effect size = –0.11, $P > .05$
Roehers and Karst,[34] 2004; quasi-experimental (pretest/posttest); exercise combined	N = 31 (20 F/11 M); all progressive MS, SPMS: NR, PPMS: NR; EDSS, 1.5-8; dropout, 12 (39%)	Aquatic exercise intervention (n = 31): endurance, strengthening, and balance exercises delivered in pool by PT students; exercises modified depending on functional ability; 12 wk, 2 session/wk, 60 min	MFIS (secondary); 0, 12 wk	MFIS: Baseline: 48.7 ± 12.1; Postintervention (final value): 43.5 ± 15; Pre/postintervention: $P = .035$

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Table 2. **Characteristics of included articles** (page 2 of 3)

Study; design; intervention	Sample details	Intervention type, delivery mode, duration, frequency	Fatigue outcome measure; time points	Main findings[a]
Pilutti et al,[35] 2011; quasi-experimental (pretest/posttest); exercise aerobic	N = 6 (4 F/2 M); SPMS: 1 (17%), PPMS: 5 (83%); EDSS, 5.5-8; dropout, 0 (0%)	BWSTT (n = 6); Percentage body weight support and treadmill speed individualized to each participant in relation to posture and comfort when walking; Training progressed initially by increasing treadmill speed followed by reducing body weight support; 12 wk, 3 sessions/wk, 30 min	MFIS (secondary), MSQOL-54 energy subscale (secondary); 0, 12 wk	MFIS (total): Baseline: 43.5 ± 12.26; Pretest/posttest: MD = –13.3 ± 20.96, effect size (95% CI) = –0.93 (–30.11 to 3.44), *P* = 0.22. MFIS (physical): Baseline: 24.3 ± 5.8; Pretest/posttest: MD = –5.9 ± 9.27, effect size (95% CI) = –0.8 (–13.33 to 1.5), *P* = .22. MFIS (cognitive): Baseline: 14.6 ± 8.92; Pretest/posttest: MD = –6.8 ± 9.46, effect size (95% CI) = –0.78 (–14.32 to 0.82), *P* = .14. MFIS (psychosocial): Baseline: 4.7 ± 2.58; Pretest/posttest: MD = –0.7 ± 3.08, effect size (95% CI) = –0.28 (–3.13 to 1.8), *P* = .62. MSQOL-54 (energy): Baseline: 32 ± 19.64; Pretest/posttest: MD = 19.3 ± 12.56, effect size (95% CI) = 0.93 (9.28 to 29.39), *P* = .01
Briken et al,[36] 2014; RCT; exercise aerobic	N = 47 (24 F/18 M)[b]; SPMS: 31 (74%), PPMS: 11 (26%); EDSS, 4-6; dropout, 5 (11%)	Aerobic exercise, 4 trial arms: arm ergometry (n = 12), rowing (n = 12), cycling (n = 12), waitlist control (n = 11); Intervention delivered in medical center by physiotherapist; Training intensity tailored to each participant depending on performance during submaximal aerobic fitness assessment; 8-10 wk, 2-3 sessions/wk, 15-45 min	MFIS (secondary); 0, 10 wk	MFIS: Baseline: Arm ergometry: 45.00 ± 14.73, rowing: 35.27 ± 13.86, cycling: 35.27 ± 13.86, C: 38.00 ± 15.15; Between group: Arm ergometry vs C: *P* = .013, rowing vs C: *P* > .05, cycling vs C: *P* > .05, all interventions vs C: *P* = .019
Skjerbaek et al,[37] 2014; RCT; exercise aerobic	N = 11 (8 F/3 M); SPMS: 8 (73%), PPMS: 3 (27%); EDSS, 6.5-8; dropout, 1 (9%)	Upper body endurance training (n = 6): standard care plus 10 sessions of upper limb arm ergometry over 4 wk consisting of 6 × 3-min intervals at target heart rate corresponding to 65%-75% of VO_{2peak}; Control (n = 5): 4 wk of individualized multidisciplinary inpatient rehabilitation delivered in MS hospital	FSMC (secondary); 0, 4 wk	FSMC (total): Baseline: I = 65 ± 18.5, C = 53 ± 16.3; Within group (MD): I = –2.2 ± 8.7, C = –2.6 ± 7.9; Between groups: *P* = .94. FSMC (motor): Baseline: I = 36 ± 7.9, C = 29 ± 8; Within group (MD): I = –2.8 ± 5.6, C = –2 ± 5.3; Between groups: *P* = .82. FSMC (cognitive): Baseline: I = 29 ± 10.9, C = 23.8 ± 9.1; Within group (MD): I = 0.6 ± 3.6, C = –0.6 ± 2.7; Between groups: *P* = .57
van der Linden et al,[38] 2014; quasi-experimental (pretest/posttest); exercise other	N = 15 (8 F/7 M); all progressive MS, SPMS: NR, PPMS: NR; EDSS, 7-8; dropout, 1 (7%)	Seated Pilates (n = 15) exercises focused on core strengthening, with elements of upper limb strengthening exercises and home exercise program to be done 15 min daily; Delivered by qualified Pilates instructor at 2 community centers; Weeks 1-6: 2 sessions/wk, 60 min, weeks 7-12: 1 session/wk, 60 min	FSS (secondary); 0, 6, 12 wk	FSS: Baseline: 5.2 ± 1.3; Week 6 (final value) = 4.7 ± 1.6; Week 12 (final value) = 4.9 ± 1.7; Baseline, week 6: *P* = .132; Baseline, week 12: *P* = .295
Bogosian et al,[39] 2015; RCT; behavioral	N = 40 (22 F/18 M); SPMS: 23 (58%), PPMS: 17 (42%); EDSS mean ± SD, 6.5 ± 1.5; dropout, 7 (18%)	Mindfulness intervention to manage distress; Group-based video conference adapted from Mindfulness-Based Cognitive Therapy course book (n = 19); Waitlist control (n = 21); Intervention delivered to groups of 5 people by health psychologist with training in delivering mindfulness sessions; 8 wk, 1 session/wk, 60 min	FSS (secondary); 0, 8, 12 wk	FSS: Baseline: I: 39.91 ± 14.45, C: 48.29 ± 12.24; Between groups posttest: MD = –4.20, effect size (95% CI) = –0.3 (–9.84 to 1.45), *P* = .145; Between groups 3 mo: MD = –4.07, effect size (95% CI) = –0.29 (–10.69 to 2.56), *P* = .302

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Table 2. Characteristics of included articles (page 3 of 3)

Study; design; intervention	Sample details	Intervention type, delivery mode, duration, frequency	Fatigue outcome measure; time points	Main findings[a]
Pilutti et al,[40] 2016; quasi-experimental (pretest/posttest); exercise aerobic	N = 12 (6 F/6 M); SPMS: 8 (67%), PPMS: 4 (33%); EDSS, 6-8; dropout, 2 (17%)	TBRST (n = 6), BWSTT (n = 6); Participants instructed to exercise at 3-5 Borg rating of perceived effort (10-point scale); 12 wk, 3 sessions/wk, 30 min	MFIS (secondary); 0, 12 wk	MFIS (total): Baseline: TBRST = 35.6 ± 9.21, BWSTT = 54.2 ± 9.71; Within groups (effect size): TBRST = –1.04, BWSTT = –1.23; Pre/posttest (groups combined): $P > .05$. MFIS (physical): Baseline: TBRST = 22.8 ± 5.03, BWSTT = 27 ± 1.66; Within groups (effect size): TBRST = –1.05, BWSTT = –1.58; Pretest/posttest (groups combined): $P \leq .05$. MFIS (cognitive): Baseline: TBRST = 9.2 ± 6.72, BWSTT = 22.4 ± 7.08; Within groups (effect size): TBRST = –0.59, BWSTT = –0.8; Pretest/posttest (groups combined): $P > .05$. MFIS (psychosocial): Baseline: TBRST = 3.6 ± 1.47, BWSTT = 4.8 ± 1.44; Within groups (effect size): TBRST = –0.46, BWSTT = –1.03; Pretest/posttest (groups combined): $P \leq .05$
Straudi et al,[41] 2016; RCT; exercise task orientated	N = 58 (34 F/18 M)[b]; SPMS: 36 (69%), PPMS: 16 (31%); EDSS, 6-7; dropout, 9 (16%)	RAGT (n = 30): BWSTT with robotic-driven gait orthosis, starting with 100% guidance from orthosis and 50% body-weight support, and 10% adjustments were made to both settings as training progressed. Treadmill speed varied between 0.1-3 km/h; CWT (n = 28): lower limb muscle stretching and strengthening, motor coordination, gait, and balance exercises; 6 wk, 2 sessions/wk, 60 min	FSS (secondary), SF-36 vitality subscale (secondary); 0, 3, 6, 12 wk	FSS: Baseline: RAGT = 5.78 ± 1.11, CWT = 5.69 ± 1.27; MD (vs baseline): Week 3: RAGT = –0.13 ± 0.83, $P > .05$; CWT = –0.04 ± 1.36, $P > .05$; Week 6: RAGT = –0.23 ± 1.05, $P > .05$; CWT = 0.01 ± 1.15, $P > .05$; Week 12: RAGT = 0.18 ± 0.87, $P > .05$; CWT = 0.18 ± 1.16, $P > .05$. SF-36 vitality: Baseline: RAGT: 45.37 ± 17.92, CWT: 44.20 ± 20.45; MD (vs baseline): Week 3: RAGT = 0.93 ± 10.29, $P > .05$; CWT = –3.20 ± 18.98, $P > .05$; Week 6: RAGT = 7.41 ± 13.40, $P < 0.01$; CWT = 2.20 ± 16.40, $P > .05$; Week 12: RAGT = –1.78 ± 19.58, $P > .05$; CWT = 0.20 ± 19.23, $P > .05$

Abbreviations: BWSTT, body-weight–supported treadmill training; C, control group; CWT, conventional walking therapy; EDSS, Expanded Disability Status Scale; F, female; FIS, Fatigue Impact Scale; FSS, Fatigue Severity Scale; FSMC, Fatigue Scale for Motor and Cognitive functions; I, intervention group; IMT, inspiratory muscle training; M, male; MD, mean difference; MFIS, Modified Fatigue Impact Scale; MS, multiple sclerosis; MSQOL-54, Multiple Sclerosis Quality of Life–54; NR, not reported; OT, occupational therapist or therapy; PPMS, primary progressive multiple sclerosis; PT, physical therapist or therapy; RAGT, robot-assisted gait training; RCT, randomized controlled trial; SF-36, Medical Outcomes Study 36-item Short Form Health Survey; SPMS, secondary progressive multiple sclerosis; TBRST, total-body recumbent stepper training; VO_{2peak}, peak oxygen uptake.
[a]Descriptive baseline and final values presented as mean ± SD unless stated otherwise.
[b]Demographics characteristics of participants who dropped out are not reported.
[c]Values presented as mean ± SE.

Quality Assessment

Total quality assessment scores ranged from 15 to 25 (Table 3), and no study was excluded based on the results of the quality assessment. Only seven articles reported adverse events,[31,33,34,37,38,40,41] seven adjusted for confounding variables and loss to follow-up,[29,30,35-37,39,41] six reported compliance with interventions,[35-40] and one included a power calculation to determine sample size.[41] Due to the nature of the interventions, none of the studies blinded participants to treatment allocation.

Sample Characteristics

Study sample sizes ranged from 6 to 111 participants, and overall 474 participants were included, 325 of whom were allocated to receive an intervention and 149 to a control condition. Expanded Disability Status Scale (EDSS) scores of study samples ranged from 1.5 to 9, and 12 articles reported participants with EDSS scores greater than 6.[29-35,37-41] Only one study used a predefined level for moderate-severe fatigue (Fatigue Severity Scale [FSS] score ≥4) as an inclusion criterion for participant recruitment.[33]

Table 3. Downs and Black[24] checklist scores for included articles

Article	Downs and Black checklist item[a]																										Total (0-28)
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	
Di Fabio et al[29]	1	1	0	1	1	1	0	0	1	1	1	0	1	0	0	1	1	1	0	1	1	0	0	0	1	1	0	16
Di Fabio et al[30]	1	1	0	1	1	1	1	0	1	1	1	0	1	0	0	1	1	1	0	1	1	0	0	0	1	1	0	17
Patti et al[31]	1	1	1	1	0	1	1	1	1	0	1	1	1	0	1	1	1	1	0	1	1	1	1	0	0	0	0	19
Klefbeck and Nedjad[32]	1	1	1	1	0	1	1	0	0	1	1	1	1	0	0	1	1	1	0	1	1	0	1	0	0	0	0	16
Vanage et al[33]	1	1	1	1	2	1	1	1	0	0	1	1	1	0	0	1	0	1	0	1	1	1	0	0	0	0	0	17
Roehrs and Karst[34]	1	1	1	1	0	1	1	1	1	1	0	0	1	0	0	1	1	1	0	1	1	0	0	0	0	0	0	15
Pilutti et al[35]	1	1	1	1	0	1	1	0	1	1	0	0	1	0	0	1	1	1	1	1	1	0	0	0	0	1	0	16
Briken et al[36]	1	1	1	1	1	1	0	0	1	1	1	1	1	0	0	1	0	1	1	1	1	0	1	0	1	1	0	19
Skjerbaek et al[37]	1	1	1	1	2	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	0	1	1	1	0	0	23
van der Linden et al[38]	1	1	1	1	0	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	0	0	0	0	0	0	18
Bogosian et al[39]	1	1	1	1	1	1	1	0	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	0	24
Pilutti et al[40]	1	1	1	1	2	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	0	1	0	0	0	0	21
Straudi et al[41]	1	1	1	1	2	1	1	1	1	1	1	1	1	0	1	1	1	1	0	1	1	0	1	1	1	1	1	25

Note: 2, criterion fully met (item 5); 1, criterion met or partially met (item 5); 0, criterion not met.
[a]Abbreviated Downs and Black checklist item descriptions: 1, hypothesis/aims/objectives reported; 2, main outcome measures reported; 3, participant characteristics reported; 4, intervention details reported; 5, principal confounders reported; 6, main findings reported; 7, variability in main outcomes reported; 8, adverse events reported; 9, loss to follow-up reported; 10, probability values reported; 11, source population representative of entire population; 12, study population representative of source population; 13, study setting representative of usual care; 14, participants blinded to intervention; 15, outcome assessors blinded; 16, no retrospective subgroup analysis; 17, analysis adjusts for different lengths of follow-up of participants; 18, statistical tests are appropriate; 19, reliable compliance with intervention; 20, outcome measures are valid and reliable; 21, recruitment of study groups from same population; 22, recruitment of participants over same period; 23, randomization of participants; 24, allocation concealment; 25, adjustment for confounding variables in main analysis; 26, adjustment for loss to follow-up in main analysis; 27, inclusion of sample size calculation.

Outcome Measures

There were seven self-reported outcome measures used across the included articles to measure the severity or impact of fatigue, and the most commonly used were the FSS (n = 4)[32,38,39,41] and the Modified Fatigue Impact Scale (MFIS) (n = 4).[34-36,40] In addition, studies also used the Fatigue Impact Scale (FIS),[31,33] the MS-Related Symptom Checklist (fatigue subscale),[30] the Fatigue Scale for Motor and Cognitive functions,[37] the 36-item Short Form Health Survey (SF-36) vitality subscale,[29,41] and the Multiple Sclerosis Quality of Life–54 energy subscale.[35] Of the 13 included articles, two stated that fatigue was the primary outcome of investigation,[30,33] and in the remaining 11 fatigue was a secondary outcome and the primary outcomes were quality of life,[29,31,34] aerobic fitness,[36,37] global measures of physical function,[35] distress,[39] temporal measures of gait,[41] lung function,[32] exercise safety,[40] and sitting balance.[38]

Intervention Types

In accordance with the definitions of interventions for this review, eight exercise,[32,34-38,40,41] two rehabilitation,[29-31] and two behavioral interventions[33,39] were described by the 13 included articles.

Of the eight exercise interventions, four were classified as aerobic exercise,[35-37,40] one as combined exercise,[34] one as task-orientated exercise,[41] and two as other exercise.[32,38] Various modes of exercise were used across the four trials of aerobic exercise: one used arm ergometry,[37] two used body-weight–supported treadmill training,[35,40] one used recumbent stepping,[40] and Briken et al[36] used arm ergometry, cycling, and rowing. Most interventions were performed at moderate intensity and were progressed through increasing the duration of training; however, the study by Skjerbaek et al[37] implemented a high-intensity interval training protocol involving 3-minute intervals working at a heart rate corresponding to 65% to 75% peak oxygen uptake.[37] In addition to aerobic exercise, the combined exercise intervention described by Roehrs and Karst[34] incorporated elements of upper and lower limb resistance exercises and was delivered in a pool by physical therapy students.

The study by Straudi et al[41] was characterized as task-orientated exercise because the intervention aimed to improve temporal gait parameters by using a robotic-assisted gait orthosis in conjunction with body-weight–supported treadmill training. The two other exercise interventions involved seated Pilates[38] and inspiratory

muscle training.[32] The seated Pilates intervention was delivered by a qualified Pilates instructor and incorporated elements of core and upper limb strengthening with a daily home exercise program.[38] Inspiratory muscle training followed a self-management program of inspiratory muscle resistance exercises that consisted of three sets of ten loaded inspirations using a threshold inspiratory muscle training device.[32]

The two behavioral intervention studies involved mindfulness[39] and energy conservation management.[33] The mindfulness intervention was delivered via a group-based video conference by a health psychologist. The content involved components of the Mindfulness-based Stress Reduction program with additional cognitive therapy exercises and "homework" tasks. The energy conservation intervention was delivered face-to-face in a group by occupational therapists and involved education regarding optimum energy use to minimize the impact of fatigue through restructuring or altering activities of daily living in accordance with Packer's energy conservation course.

Rehabilitation interventions were delivered by a multidisciplinary team consisting of physiotherapists, occupational therapists, and support services in an outpatient setting, and treatments were individualized to each participant.[29-31] In the study by Di Fabio et al,[29,30] participants received 5 hours of rehabilitation 1 day per week that consisted of physiotherapy (gait, transfer, and balance training; endurance training; range of movement exercises), occupational therapy to maintain upper limb use during activities of daily living and enhance communication skills, and support services (support groups, social work, recreation activities, falls prevention programs, seating clinics, and nutritional information). The intervention delivered by Patti et al[31] consisted of 1 hour of physiotherapy treatment 5 days per week, 30 minutes of occupational therapy and speech therapy twice per week, and support sessions on symptom self-management and goal setting. In addition to outpatient rehabilitation, Patti et al[31] included the prescription of a daily home exercise program.

Effectiveness of Interventions

Exercise

Of the studies investigating aerobic exercise interventions, Skjerbaek et al[37] reported that although Fatigue Scale for Motor and Cognitive functions scores improved in the exercise group after the intervention (mean ± SD difference, –2.2 ± 8.7), there was no significant difference between the exercise and control groups over time. Similarly, Pilutti et al[35,40] reported nonsignificant improvements in MFIS scores after the intervention (effect sizes, –0.93 and –1.04, respectively). However, Pilutti et al[35] found statistically significant changes in Multiple Sclerosis Quality of Life–54 energy subscale scores after the intervention (P = .01). The studies by Pilutti et al[35,40] and Skjerbaek et al[37] had small samples (n = 6-12) and included participants with severe disability (EDSS scores, 5.5-8). In contrast, Briken et al[36] investigated three aerobic exercise interventions in a larger population (n = 47) of participants with moderate disability (EDSS scores, 4-6) and reported that exercise significantly improved fatigue from baseline (P = .019); however, only arm ergometry demonstrated significant improvements compared with the control group (P = .013).

Of the remaining exercise interventions, no significant changes were noted in fatigue after combined exercise,[34] Pilates,[38] or inspiratory muscle training.[32] In addition, there were no significant improvements in FSS scores after the intervention or at 6-week follow-up for those receiving task-orientated exercise interventions; however, SF-36 vitality subscale scores improved after the intervention for the group receiving robot-assisted gait training (P < .01) but returned to baseline at 6-week follow-up.[41]

Behavioral

In a nonrandomized crossover trial, Vanage et al[33] investigated the use of an energy conservation course and reported a significant improvement in FIS total and subscale scores after the intervention (effect size, 0.89; P < .01) that was maintained at 8-week follow-up. However, Bogosian et al[39] reported no significant difference in fatigue scores after the intervention and at 6-week follow-up between the group receiving a mindfulness intervention and a waitlist control group. In addition to the mode of intervention, differences in results between studies may be explained by study design because Vanage et al[33] recruited participants with a clinically significant level of fatigue and used fatigue as a primary outcome, whereas Bogosian et al[39] did neither.

Rehabilitation

Di Fabio et al[30] reported that fatigue scores (MS-Related Symptom Checklist) for those receiving 52-week multidisciplinary rehabilitation were signifi-

cantly different after the intervention compared with those of waitlist controls (effect sizes, 0.46 and –0.2, respectively). From the same study, Di Fabio et al[29] also reported that SF-36 vitality subscale scores improved after the intervention for the group receiving rehabilitation (effect size, 0.3) and that fatigue in the waitlist control group increased in severity (effect size, –0.39). In the study by Patti et al,[31] those receiving 12 weeks of outpatient rehabilitation demonstrated a significant improvement in postintervention fatigue scores ($P < .001$).

Clinical Significance of Fatigue Changes

Of the outcome measures reported, MCID has been determined only for the FIS in MS populations. When anchored to measures of health-related quality of life, FIS demonstrates an MCID of 10 to 20 points.[42] Of the two included studies that used the FIS, both reported significant improvements in fatigue after the intervention (mean ± SD differences of 18.8 ± 14.3 [$P < .001$][31] and 15.7 ± 25 [$P < .01$][33]). However, although the mean change in FIS scores recorded by both studies is within the range of MCID estimates reported for the FIS, both studies reported large SDs, suggesting that these interventions may be clinically significant for only some participants.

Discussion

Overall, the evidence presented in this review is inconclusive regarding the use of exercise, behavioral, and rehabilitation interventions to manage the severity and impact of fatigue in progressive MS populations. However, the quality of evidence is generally weak due to the small number of underpowered studies with limited methodological designs.

Exercise Interventions

The evidence is inconclusive regarding the effectiveness of exercise as an intervention to reduce the severity and impact of fatigue in people with progressive MS. However, of the four studies that investigated aerobic exercise, all demonstrated improvement in fatigue impact after the intervention,[35-37,40] although only Briken et al[36] reported that changes in fatigue impact were statistically significant. The result of this review including studies of people with progressive MS is comparable with a similar review that reported that aerobic exercise improves fatigue in those with RRMS.[17] However, the studies included in this current review had small sample sizes and were underpowered to detect significant changes in fatigue. In addition, three of the studies included participants with high levels of disability (EDSS scores ≥6), which may have further influenced results as, to date, the positive evidence for the effect of exercise on fatigue has been demonstrated only in those with mild-moderate disability (EDSS scores ≤5.5),[17,43] whereas varied effects are reported in those with higher levels of disability.[27]

Comparing the effectiveness of aerobic exercise with other modes of exercise is limited by the small number of heterogeneous studies. Only four studies investigated forms of exercise other than aerobic—including aquatic therapy[34] and inspiratory muscle training[32]—and the evidence generally does not support the effectiveness of these interventions for reducing fatigue in progressive MS populations. Furthermore, none of the included studies investigated the use of resistance training, which has been demonstrated to improve fatigue in people with RRMS.[43] Consequently, although this review highlights the potential effectiveness of aerobic exercise in fatigue management for people with progressive MS, there is insufficient evidence to determine whether this is the most effective mode of exercise.

The mechanisms through which exercise may attenuate fatigue symptoms are unknown. It is hypothesized that exercise may have a neuroprotective and neuroregenerative benefit through increasing neural growth factors that modulate structural and functional central nervous system changes associated with primary MS-related fatigue.[13] In addition, exercise training may influence secondary fatigue mechanisms caused by deconditioning, sleep disorders, and depression through increasing aerobic capacity, improving sleep quality, and managing depression.[13] The immunologic biomarkers interferon γ, tumor necrosis factor α, and interleukin 1 have also been associated with fatigue in MS[44] but may have limited relevance to those with progressive MS due to the absence of a marked inflammatory response.[45]

Of the aerobic exercise interventions included, three were performed at moderate intensity for durations of 30 to 45 minutes two to three times per week.[35,36,40] Although this dose of exercise is recommended for people with mild-moderate MS,[46] there was no evidence of a dose-response relationship to suggest that this prescription is most effective in managing fatigue, particularly in progressive MS populations. Indeed, one trial investigated shorter-duration, high-intensity aerobic exercise,[37] which may hold potential in fatigue management through inducing greater improvements in aerobic

capacity over a shorter time.[47] Therefore, no conclusions regarding the optimum dose of exercise to manage fatigue in people with progressive MS can be generated from the evidence in this review.

There is also limited evidence for the long-term effectiveness of exercise interventions. Only two studies conducted follow-up measurement, neither of which reported a significant long-term change in fatigue severity compared with the baseline assessment.[32,41] Consequently, there is a need to evaluate the long-term effectiveness of exercise interventions to determine whether improvements in fatigue are sustained after the intervention period.

Despite the limited evidence for the effectiveness of exercise intervention, most studies reported low attrition rates indicating acceptability of exercise interventions in progressive MS populations. In addition, some studies confirmed that exercise interventions were feasible in populations with higher levels of disability associated with progressive MS, which is in line with evidence from a previously published review.[27]

Behavioral Interventions

Because only two studies of behavioral interventions were included in this review, it is not possible to reach any conclusions regarding their effectiveness in reducing the severity or impact of fatigue. Both studies investigated different forms of behavioral therapy interventions and reported contrasting results regarding short- and long-term effectiveness. Vanage et al[33] reported that an 8-week energy conservation course significantly reduced fatigue impact immediately after the intervention period and at 8-week follow-up, which is comparable with previous evidence from predominantly RRMS populations.[15]

In contrast, Bogosian et al[39] reported no significant difference in fatigue severity after the intervention or at 4 weeks of follow-up between those receiving a mindfulness intervention and a waitlist control group. Mindfulness is used in MS to manage somatic symptoms and improve health-related quality of life[48] and is recommended in the National Institute for Health and Care Excellence guidelines as a strategy to manage fatigue.[14] However, the mindfulness intervention implemented by Bogosian et al[39] was designed to manage distress not fatigue. Therefore, despite the association between mood disorders and fatigue,[9,49-51] the applicability of these findings to fatigue management is limited. In addition, the mindfulness sessions were delivered via video conference, which, while accommodating those with severe mobility disabilities, may limit the social benefits reported during group-based interventions delivered face-to-face.[33,52]

Rehabilitation Interventions

Although evidence from this review is positive regarding the effects of rehabilitation on fatigue, only two studies of rehabilitation interventions were included. Generally, rehabilitation interventions were individualized to each participant, goal-orientated, addressed functional performance, and were delivered by a multidisciplinary team. In both articles, changes in fatigue severity after 52 weeks of multidisciplinary rehabilitation were statistically significant, with moderate effect sizes reported for those receiving rehabilitation and worsening fatigue in the waitlist control group.[29,30] However, because this study included only two points of outcome assessment (baseline and 52 weeks), the rate at which improvements in fatigue were accumulated cannot be observed. Patti et al[31] implemented a shorter duration, higher-intensity intervention that demonstrated clinically significant improvements in fatigue impact for some participants after the intervention. Therefore, there is a need to determine the most effective duration of rehabilitation interventions.

It is acknowledged that exercise or behavioral interventions can be delivered as components of rehabilitation. However, the rehabilitation interventions included in this review were multidisciplinary and were differentiated from exercise and behavioral interventions alone because they contained additional treatment strategies, such as physiotherapy and occupational therapy, to maintain physical function. Consequently, it was not possible to identify the effectiveness of each component part of rehabilitation, for example, the effectiveness of exercise delivered as part of rehabilitation. This information is essential to constructing rehabilitation programs that are best designed to manage fatigue.

Limitations of the Evidence

There were several important limitations that affect the overall quality of evidence. First, only two studies used fatigue as a primary outcome measure,[30,33] and of these studies, only one recruited participants with clinically significant levels of fatigue (FSS score, ≥4).[33] Therefore, there is limited evidence of the effect of interventions specifically designed to manage fatigue in people with clinically significant levels of fatigue.

In addition, seven different fatigue outcome measures were used in this review, limiting the ability to directly compare results between studies. Although a meta-analysis of exercise interventions demonstrated that the selection of fatigue outcome measures did not moderate the effect of interventions,[17] there is a need for core fatigue outcome measures to enable pooling of statistical data for meta-analysis and comparison of effects between studies. In addition, MCID has been determined only for the FIS. Therefore, the MCID of the MFIS and FSS should be determined to establish the clinical significance of changes in fatigue severity and impact.

Finally, most studies were underpowered to detect significant changes in fatigue. In addition, due to the inclusion of quasi-experimental studies, several studies were unable to control for confounding variables, which may have accounted for the heterogeneous treatment response reported within and between studies. Furthermore, adverse events and compliance with interventions were poorly reported across studies, limiting the ability to determine the safety and efficacy of interventions in clinical practice.

Limitations of the Review

There were many other studies that investigated the effectiveness of fatigue management interventions in people with progressive MS; however, these studies were excluded because the results for people with progressive MS could not be specifically identified. In addition, the overall quality of evidence in this review is limited by the inclusion of quasi-experimental studies, which are less methodologically rigorous and introduce risk of selection bias. Furthermore, due to the inclusion of quasi-experimental studies and the heterogeneity in outcome measures and interventions used between studies, it was not feasible to conduct a meta-analysis, and results were generated by narrative synthesis.

PRACTICE POINTS

- Exercise, behavioral interventions, and rehabilitation demonstrate the potential to manage fatigue in progressive MS populations.
- Evidence in this review suggests that aerobic exercise can improve fatigue in people with progressive MS; however, the optimal dose was not determined.
- Further evidence is required to determine the effectiveness of these interventions in studies that use fatigue as the primary outcome and recruit people who have high levels of fatigue.

Conclusion

There is insufficient evidence regarding the effectiveness of nonpharmacologic interventions in reducing the impact and severity of fatigue in people with progressive MS. This review suggests that exercise, behavioral interventions, and rehabilitation may have the potential to manage fatigue. However, future, adequately powered, rigorous trials of interventions to manage fatigue in populations with severe levels of fatigue are required. In addition, future studies should clearly identify the specific results for people with progressive MS due to the limited available evidence for this population. □

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