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Exercise Approaches to Ameliorate Fatigue in People with Multiple Sclerosis

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Abstract

Objective: People with multiple sclerosis (MS), a chronic disease of the central nervous system without a known cure, often experience fatigue that affects their quality of life. The goal of this article was to review the available literature on the role of different intervention modalities' efficacy in reducing the effects of fatigue in patients with MS.

Methods: We reviewed 47 studies available in PubMed, Academic Search Premier (EBSCO host) and Cochrane databases until March 2013 that focus on the role of the mind and body approach and exercises in minimizing fatigue in individuals with MS.

Results: The reviewed studies showed the effectiveness of Yoga, Tai Chi and neurocognitive exercises based interventions in ameliorating levels of fatigue and improving quality of life in individuals with MS.

Conclusions: This focused review suggests that a variety of approaches involving Mind and Body interventions and exercise modalities can be used individually or in combination to deal with fatigue in individuals with MS. The review also provides a basis for further research focused on evaluation of the effectiveness of each of these modalities in resolving the effects of fatigue in patients with MS.

Keywords: Multiple sclerosis; Fatigue; Mind and Body Therapies; Exercise Therapy

Introduction

Multiple sclerosis (MS) is an inflammatory autoimmune disease caused due to damage to the myelin sheath covering nerve cells. Disruption of the myelin sheath results in slowing of neural transmission and causes the nerves to fatigue rapidly. The lesions are disseminated in the white matter and cause a wide range of impairments that can impact sensory, motor and/or cognitive functions [1]. MS largely affects young adults between ages 20 and 40, Caucasians, and those who live in areas away from the equator and at high altitudes [2]. The disease is more common in women than in men [3]. Genetics, environmental factors and viral infections are all known to be contributing factors. However, the exact causes of MS are unknown, and there is no remedy to this disease.

Common MS symptoms include weakness, fatigability, depression, spasticity, visual disturbances and parasthesias. Fatigue is one of the most bothersome symptoms in patients with MS as the disease progresses [4].

Fatigue associated with MS is defined in the literature as, "Lack of physical and/or mental energy that is perceived by the individual to interfere with usual and desired activities" [5]. Sixty-five to ninety-seven percent of individuals with MS experience fatigue on a daily basis; it occurs irrespective of the disease duration and the age of the patient. Almost 15-40% of patients with MS describe fatigue as the most troubling symptom (reviewed in [6]). In a survey of 1300 people with MS, conducted in England, 92% of the people experienced fatigue and identified it as the most common symptom, and of those surveyed 74% reported that it interferes with their activities of daily living. It is also reported in the literature that fatigue occurs in individuals with MS without any warning. It resembles flu like exhaustion, and it is not always associated with the severity of the disease [7].

There are multiple reasons fatigue occurs in individuals with MS including the disease process itself and also factors such as depression, physical activity, infection, poor sleep, spasticity, and pain [5,8]. Fatigue in individuals with MS can also occur as a result of failure of central activation, damage to peripheral nerve conduction, or simply the inability to generate force during exercise [9,10]. Side effects of different medications like analgesics, antidepressants, anticonvulsants as well as anti-inflammatory medicines may also be a reason individuals with MS experience fatigue [7].

Different interventions are used to minimize the effects of fatigue. Among them are activity pacing and lifestyle management techniques [3], drug therapy involving Amantadine, Pemoline, Potassium Channel blockers and antidepressants [3], rehabilitation in form of exercise therapy [11], occupational therapy [12], and alternative therapies such as Yoga and acupuncture/acupressure [3]. The literature on the efficiency of these therapies in resolving fatigue in individuals with MS is not very extensive. In addition, while there are published reviews on the effects of exercise therapy on fatigue in individuals with MS [5,13,14], no prior publications systematically reviewed the role of a mind and body approach in mitigation of fatigue in individuals with MS.

The objective of this paper was to summarize the role of different therapies in resolving fatigue in the MS population. Forty-seven articles were selected from PubMed, Academic Search Premier (EBSCO host) online literature sources and Cochrane databases (Figure 1).

The search was conducted using the terms "multiple sclerosis",

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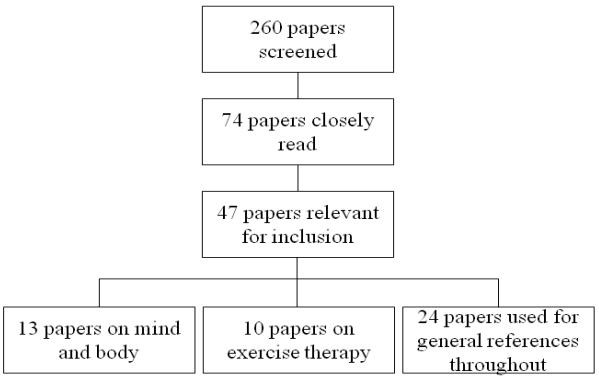

Figure 1: Flowchart showing study selection.

"fatigue", "training", "exercise", and "mind and body." A meta-analysis was not performed because of the heterogeneity of the study conditions and outcome measures. The results of the systematic analysis are presented below with a focus on activities that have a direct effect in resolving fatigue in individuals with MS as well as on activities that might resolve fatigue in MS indirectly (Figure 1).

Interventions Focusing on the Mind and Body Approach

Mind-body medicine focuses on the communication between the mind and body and the powerful ways in which emotional, mental, social, and spiritual factors can directly affect health [15]. Meditation, relaxation and breathing techniques, Yoga, Tai Chi, hypnosis, visual imagery, and spirituality are all considered mind-body interventions [16]. There is substantial literature on the mind's capacity to affect bodily function and symptoms in individuals with cancer [17,18], hypertension [19], coronary heart disease [20], and diabetes [21]. However, the amount of literature on the role of the mind and body approach in alleviating fatigue in individuals with MS is much smaller. Below we present the available information on the use of Yoga, Tai Chi, and Neurocognitive therapy as well as Energy Conservation techniques for reducing fatigue in individuals with MS.

Yoga

Yoga is a form of intervention that combines physical exercises and mediation. Yoga's conceptual background originates in Indian philosophy. There are different types of yoga in terms of physical and spiritual practices like Iyengar, Viniyoga, Sivananda, etc. A typical yoga session consists of practicing a sequence of postures, breathing techniques, and mental concentration/meditation, usually lasting for 1 or 2 hours per session [22]. The most common benefits that practitioners of yoga can experience include an increase in muscle strength, flexibility, and range of motion, energy, relaxation and an improved sense of well-being. Yoga also helps to decrease pain, improve sleep quality, reduce stress, improve control over physiological parameters [22], as well as improve cognitive function in individuals with MS [23]. Moreover, it was reported that yoga has been instrumental in showing improvements in anxiety and depression, and produce positive psychological impacts in individuals with neurological disorders [24].

While yoga is reported among the six mostly used complementary therapies in the treatment of MS [25], the reports on the effects of yoga on fatigue management in individuals with MS are scarce. Nevertheless, significant improvements in measures of fatigue were seen as a result of yoga interventions in individuals with MS as compared to a control group which performed stationary bicycle exercises [23]. However, when the effects of yoga were compared to the effects of sports climbing in individuals with MS, the yoga group did not show any significant improvements in fatigue, while the sport climbing group showed a 32.5% reduction in fatigue as measured on the Modified Fatigue Impact Scale (MFIS) [26]. On the contrary, community exercise programs incorporating exercise in form of yoga have led to beneficial effects related to resolving fatigue. In a study involving the following four groups of individuals with MS, (1) yoga (n=63), (2) fitness group led by an instructor (FI-led group) (n=67), (3) fitness group led by a physiotherapist (PT-led group) (n=63), and (4) control group (n=49), improvements in fatigue were observed in groups 1, 2 and 3 as compared to the group 4 i.e. control group [27]. It is important to note that in the follow-up assesment improvements in the walking distance on the 6 minute walk test (6MWT) were seen in the yoga group [28] (Table 1).

Tai Chi

Tai Chi is yet another form of exercise that promotes the association between mind and body. Tai Chi involves the performance of slow, continuous and graceful meditating movements that are in rhythm with one another and flow into one another ensuring that body is in continuous motion [16,29]. The literature reports positive effects of practicing Tai Chi on psychological indicators including enhanced well-being, stress reduction, and decreased anxiety, depression and mood disturbance in healthy populations [30]. Multiple studies have also shown an improvements in balance and reduction of falls in the elderly following Tai Chi practice [31]. Surprisingly, while a substantial body of literature exists on the role of Tai Chi on well-being in patients with cancer [32-35], chronic fatigue syndrome [36], and fibromyalgia [30,37,38], there are only a limited number of studies focusing on the effects of Tai Chi on fatigue in patients with MS (Table 2).

Only two studies were found that looked at the effects of Tai Chi on fatigue in individuals with MS. Practicing Tai Chi for two months daily was associated with improvements in balance, lower depression, as well as some improvements in fatigue in individuals with MS [4]. Another study focused on the effects of 40 Tai Chi sessions performed in a swimming pool. It was shown that there was a significant reduction in fatigue in individuals with MS participating in the Tai Chi classes as compared to the control group who performed breathing exercises and contraction relaxation exercises in the therapy room [39]. The above study also showed improvements in the disability level in both the Tai Chi and control groups until weeks 20 and 24. In the later follow-up, however, only the group performing Tai Chi exercises continued to show the improvements. Moreover, depression level, quality of life and disability was improved only in the Tai Chi group as compared to the control group [39] (Table 2).

Neurocognitive approach

The primary principle in neurocognitive rehabilitation is to utilize the patient's strength to overcome weakness. Neurocognitive therapy is based on the hypothesis that the central nervous system can improve movement in pathological conditions through correct activation of the cognitive processes of the patient including attention, memory, language and motor imagery. This therapy mainly involves exercises in which the patient has to solve cognitive or motor problems through movements of the body segments with help from the therapist [40].

The effect of neurocognitive therapy was evaluated in a group of individuals with MS (N=20) who had complaints of fatigue [40].

Reference	N	Study Design	Inclusion Criteria	Duration of Intervention	Study Groups	Intervention	Outcome Measures used	Effect of Interventions on Fatigue	Comments
Yoga									
Oken BS et al. 2004 [23]	69	RCT	Score of 6 or less on EDSS. Ability to walk 100 meters with unilateral support	48 weeks	Group1:Yoga Group 2: Stationary Bike Group 3: Control Group	Group 1: 90 min of Yoga classes Group 2: Bicycling on recumbent or dual stationary bicycle Group 3: Waiting list (control group)	Battery of cognitive measures focused on attention, physiologic measures of alertness, Profile of Mood States, State-Trait Anxiety Inventory, MFI, and SF-36.	Groups 1 and 2 showed improvement in measures of fatigue in the form of Energy and Fatigue on SF-36 and general Fatigue on MFI compared to group 3	Changes in mood as a result of any of the intervention were unclear
Velikonja et al. 2010 [26]	20	RCT	Score of 6 or less on EDSS. EDSS pyramidal score >2	10 weeks	Group 1: Yoga Group 2: Sports climbing	Group 1: Hatha Yoga Group 2: Climbing on climbing wall with an inclination of 90 degrees and height of 5 m	Modified Ashworth's scale, Mazes subtest, Tower of London Test, Brickenkamp d2 test, Epidemiologic Studies period. Depression Scale, MFIS	Group 1 did not show significant reduction in fatigue Group 2 showed reduction in fatigue (p=0.015)	No differences in spasticity, cognitive function and mood
Garrett et al. 2013 [27]	242	RCT	Ability to walk outdoors with unilateral support	10 weeks	Group 1: Yoga (n=63) Group 2: Fitness instructor led (n=67) Group 3: Physiotherapist led (n= 63) Group 4: Control Group (n=49)	Group 1: Asanas, Breathing and Relaxation exercises Group 2: Progressive resistance and aerobic exercises Group 3: Resistance as well as aerobic exercises Group 4: Told to maintain current habits without any changes	MSIS 29v2 physical component, MSIS 29v2 psychological component, MFIS and the 6-Minute Walk Test	Significant improvements in fatigue in groups 1, 2, and 3 as compared to the control group.	
Garrett et al. 2013 [28]	121	RCT	Ability to walk outdoors with unilateral support	Follow up after 12 weeks	Group 1: Yoga (n=63) Group 2: Fitness instructor led (n=67) Group 3: Physiotherapist led (n=63) Group 4: Control Group (n=49)	Group 1: Asanas, Breathing and Relaxation exercises Group 2: Progressive resistance and aerobic exercises Group 3: Resistance as well as aerobic exercises Group 4: Told to maintain their current habits without any changes	MSIS 29v2 physical component, MSIS 29v2 psychological component, MFIS and the 6-Minute Walk Test	Improvements maintained at follow up	Group 1 showed improvement in the 6MWT in the follow-up phase

N: Number of Subjects; RCT: Randomized Controlled Trial; EDSS: Expanded Disability Status Scale; MFI: Multidimensional Fatigue Inventory; SF-36-Short form health –related quality of live survey; MFIS: Modified Fatigue Impact Scale; MSIS: Multiple Sclerosis Impact Scale

Table 1: Effect of Yoga on Fatigue in individuals with MS.

There was an improvement in fatigue scores as well as quality of life in these individuals after the neurocognitive therapy. Notably, this improvement was maintained during the 6 month follow-up assessment [40]. Moreover, the effects of online cognitive behavioral therapy (CBT) on reduction of fatigue were seen in the individuals with MS. The experimental group was provided with 8 weekly interactive sessions each lasting for 25 to 50 min; these sessions included patient self-assessment which was used to tailor the program according to the individual's progress and capabilities. The results of the study showed a decrease in fatigue. In addition there were improvements in anxiety, depression levels and QOL in the experimental group that was provided with online cognitive behavioral therapy [41] (Table 2).

Energy conservation strategies/techniques

Energy conservation (EC) strategies are a form of non-pharmacological management that are used in people with chronic illnesses for managing fatigue [42,43]. EC strategies include analysis and modification of activities to reduce the energy spent on performing activities, attaining balance between work and rest, using the body efficiently, delegating some activities to others, organization of the workplace and using assistive technologies to conserve energy [43]. An energy conservation course has been shown to be beneficial to the people with progressive multiple sclerosis [44].

A 19 weeks community based energy conservation course (that

Reference	N	Study Design	Inclusion Criteria	Duration of Intervention	Study Groups	Intervention	Outcome Measures used	Effect of Interventions on Fatigue	Comments
Tai Chi									
Mills et al. 2000 [4]	8	Comparative	Ability to come to the hospital Ability to fill out the questionnaires Experiencing at least one ongoing symptom related to MS	8 weeks	2 month baseline f ollowed by 2 month i ntervention	Tai Chi/QiGong along with the teaching QiGong self-massage TuiNa and daily home practice for 30 min	Profile of Mood states, Physical symptoms, single leg standing time	Improvements in fatigue post intervention on a 21-item symptom checklist	Statistically significant differences in the pre-post measures of depression and balance
Castro-Sanchez et al. 2012 [39]	73	RCT	EDSS score less than or equal to 7.5. Visual Analogue Scale pain score (VAS) >4	20 weeks	Group 1: Tai Chi Group 2: Relaxation	Tai Chi exercises with 16 movements or postures performed in shoulder depth water along with warm-up and relaxation periods.	Pain, disability, spasm, depression, fatigue, and autonomy	Improvements in fatigue in the Tai-Chi group	Improvements were also seen in the spasm, disability, depression and autonomy measures
Neurocognitive Therapy									
Catalan et al. 2011 [40]	20	Comparative	EDSS between 1 and 6 Fatigue as a complain	5 weeks	Pre and Post assess-ments were performed in addition to 6 month follow-up	Neurocognitive exercises 2 times a week	FSS, MFIS, MSQoL54, EDSS, and MSFC	Improvement in fatigue scores	
Mosss et al. 2012 [41]	40	RCT	Significant fatigue indicated by a score > 4 on the Fatigue scale using the binary scoring method. Ability to Ambulate with or without a stick for at least 100 m.	8 weeks	Group1: Experimental (n=23) Group 2: Control (n=17)	25-50 min of interactive session including self assessments along with 3 telephone support sessions	Questionnaires assessing fatigue, mood, quality of life and service use	Improvement in fatigue in the experimental group	Significant group differences on anxiety ($p < 0.001$) and depression ($p < 0.001$).

N: Number of Subjects; RCT: Randomized Controlled trial; FSS: Fatigue Severity Scale; MFIS: Modified Fatigue Impact Scale; EDSS: Expanded Disability Status Scale; MSFC: MS Functional Composite; MSQoL54: MS Quality of Life

Table 2: Effect of Tai Chi and Neurocognitive Therapy on Fatigue in Individuals with MS.

included addressing issues like importance of rest, proper body mechanics, ergonomic principles, environmental modification, activity analysis and modification) showed that there was a significant reduction in the impact of the fatigue, increased self-efficacy and improved quality of life [45]. Moreover, the outcomes of the surveys given to the study participants before and after the study, showed that 82% of the study participants applied 6 or more energy conservation strategies and 35% applied 10 or more strategies after the course [45]. Another randomized controlled study showed that a 6 week energy conservation course had a positive impact on fatigue, quality of life and self-efficacy in people with MS. The intervention mainly included lectures, discussions, short term and long term goal setting, practice activities and homework activities to assist participants in understanding and utilizing the energy conservation principles in daily activities. As a result of this intervention there was a reduction of fatigue (confirmed by significant changes in the physical and social subscales of the Fatigue Impact scale). In addition, an increase on the Vitality subscale of the SF-36 was reported in the experimental group compared to the group of individuals with MS not taking the course. Moreover, participants' self efficacy for performing energy conservation strategies increased significantly as a result of taking the course [43] (Table 3).

Another study used a teleconference approach to deliver the energy conservation course to community dwelling individuals with MS. Six teleconference sessions were administered one time per week. The results of the study revealed that there was a significant reduction in fatigue severity, fatigue impact and body pain, and an improvement in the general health component of QOL [46].

Significant improvements were also seen in the cognitive and physical sub scores of the MFIS along with improvements in sleep quality and depression in individuals with MS after a six-week energy conservation course [47].

The feasibility of an energy conservation program to manage fatigue in persons with MS was recently tested in a randomized controlled trial involving 23 individuals with MS [48]. The outcome was that an energy conservation program was feasible and welcomed by the people with MS.

It is important to note that the skills learned during an energy conservation program were retained for quite some time. Thus, it was described that improvements were maintained at the 6 week and 3 month follow-up periods, [48] and also at the 7-9 month follow-up [47] (Table 3).

Exercise Therapy

Exercise therapy includes stretching to reduce stress on joints, core stability exercises to strengthen the muscles of the trunk, back and abdomen, hips, legs and arms, walking and running related activities and aerobic exercises, as well as many other forms of activity [49]. The

Reference	N	Study Design	Inclusion Criteria	Duration of Intervention	Study Groups	Intervention	Outcome Measures used	Effect of Interventions on Fatigue	Comments
Mathiowet et al. 2001 [45]	54	Repeated measures with control and experimental interventions	Functionally literate Score ≥ 4 on FSS Independent in self care activities	19 weeks	Group 1: Experimental Group 2: Control	Energy conservation course	Fatigue Impact Scale (self-report measure of fatigue's impact on cognitive, physical, social functions), Self-Efficacy Gauge (self-report measure of confidence in ability to perform specific behaviors), and Medical Outcomes Study Short-Form Health Survey (QOL measure)	Significant reduction in impact of fatigue	Increases in self-efficacy and improvements in QOL.
Mathiowet et al. 2005 [43]	130	RCT	Functionally literate Score ≥ 4 on FSS Independent in self care activities	6 weeks	Group 1: Immediate intervention Group 2: Delayed control	Energy conservation course	Fatigue Impact Scale, SF-36 and Self-Efficacy for Performing Energy Conservation Strategies	Reduction of Fatigue	Improvement on the SF-36 Vitality subscale. Self efficacy increased significantly from pre treatment measures.
Finlayson 2005 [46]	29	Comparative	Functional English literacy and FSS ≥ 4.	6 weeks	Pre and post intervention assessments	Energy conservation course	Fatigue severity, fatigue impact, health related quality of life, self-efficacy for performing energy conservation strategies, and use of energy conservation behaviors	Significant reductions in fatigue severity, fatigue impact, and improvements in the bodily pain and general health aspects of quality of life	
Sauter et al. 2008 [47]	32	Longitudinal study	Reported suffering from fatigue for 6 months, no relapse or cortisone therapy for 4 weeks	6 weeks	Group 1: Experimental Group 2: Control	Energy conservation course	FSS, MFIS, Pittsburg Sleep Quality Index and a self scale rating of depression and EDSS and MSFC	Improvement (group 1) in the total score, cognitive and physical scores on the MFIS.	No improvement in the FSS, MS s pecific fatigue scale and psychological fatigue impact scale. Sleep quality and depression scores improved
Garcia et al. 2013 [48]	23	RCT	Confirmed diagnosis of MS, independent in ADLs, EDSS ≤ 6, a score of ≥ 6 on RMI	5 weeks	Group 1: Control Group 2: Intervention	Energy conservation course	Recruitment and adherence, fatigue impact scale, FSS, MSIS-29, MS self efficacy scale, Beck's depression scale-fast screen and Epworth sleepiness scale	Significant improvements in the fatigue impact scale scores in the intervention group. Improvements were maintained in the follow-up period	

N-number of subjects; RCT-Randomized Controlled trial; FSS- Fatigue Severity Scale; MFIS- Modified Fatigue Impact Scale; EDSS-Expanded Disability Status Scale; MSFC- MS Functional Composite

Table 3: Effect of Energy Conservation Techniques on Fatigue in individuals with MS.

role of exercise therapy in the improvement of the lives of individuals with neurological disorders has been well documented. However, the number of publications on the effect of exercise in rehabilitation of individuals with MS is substantially smaller. This is partially because patients with MS for a long period of time were recommended not to participate in exercise activity due to a possible worsening of symptoms and fatigue [50]. However, recent literature suggests that exercise programs can improve exercise capacity, activity level, and quality of life (QOL) in individuals with MS [11,51-53]. Given the fact that using exercise as a treatment modality to reduce fatigue in individuals with MS is a relatively new approach, the number of papers related to this issue is not extensive. Below, we present a review of the literature on the effect of resistance, aerobic and aquatic exercises in the management of fatigue in individuals with MS.

Resistance exercises

Literature reports that individuals with MS are capable displaying positive improvements with resistance training. An eight-week exercise program demonstrated that individuals with MS can indeed participate in the resistance training. After training there was a reduction in the self reported fatigue assessed with the MFIS ($p<0.05$), a decrease in the self reported EDSS scores, and improvements in ambulation following the training program [54]. Progressive introduction of a resistance program for patients with MS has also been shown to enhance muscle force production, muscle endurance, functional activity participation like walking, and also improve overall psychological function. Moreover, a reduction in the perceived impact of fatigue on physical function has been reported [55]. In addition to the beneficial effect of alleviating fatigue, progressive resistance exercises have also led to improvements in mood and quality of life, along with an improvement in fatigue scores. What is more important is that the beneficial effect was maintained by study participants for at least 12 weeks after the end of the intervention [56] (Table 4).

Aerobic exercises

Aerobic exercises in form of endurance training performed by patients with MS showed that there were improvements in mobility and disability in people with moderate MS [57]. There was also a reduction in the levels of fatigue reported by the participants compared to levels of fatigue reported at the beginning of the training. For example,

Reference & Year	N	Study Design	Inclusion Criteria	Duration of Intervention	Study Groups	Intervention	Outcome Measures used	Effect of Interventions on Fatigue	Comments
Resistance Exercises									
White et al. 2004 [54]	8	Comparative	EDSS score between 1 and 5	2 times per week for 8 weeks	One group with pre and post interventions	Knee flexion, extension and plantar flexion exercises. Initially one set of 8-10 reps at 50% MVC followed by one set of 10-15 reps at 70% MVC. The resistance was increased by 2-5% when 15 reps were reached	Isometric strength of quadriceps. hamstrings, plantar flexors and dorsiflexors, MRI of thigh, walking speed (25ft), number of steps in 3 min and self reported fatigue and disability measured pre and post	Self reported fatigue reduced ($p<0.05$)	Improvement in ambulation. Patients with MS made positive adaptation to the resistance exercises
Dodd et al. 2011 [68]	76	RCT	Mild to moderate walking disabilities	2 times per week for 10 weeks	Group 1: Intervention (n=39) Group 2: Control (n=37)	Leg press, knee extension, calf raise, leg press and reverse leg press exercises. The exercises were performed in sets of 2 and were repeated for 10-12 times	Two minute walk test, Modified fatigue index scale, Multiple Sclerosis spasticity scale-88 and 1 Repetition Maximum	Physical fatigue reduced	No improvements in ambulation. However improvements in muscle endurance, strength and QOL
Dalgas et al. 2010 [56]	31	RCT	EDSS between 3.0 and 5.5, able to walk >100 m and participate in resistance training	2 times per week for 12 weeks with a post study follow-up for 12 weeks	Group 1: Exercise (n=16) Group 2: Control (n=15)	Week 1–2: three sets of 10 repetitions at a load of 15 RM; Week 3–4: three sets of 12 repetitions at a load of 12RM; Week 5–6: four sets of 12 repetitions at a load of 12RM; Week 7–8: four sets of 10 repetitions at a load of 10RM; Week 9–10: four sets of eight repetitions at a load of 8RM, Week 11–12: three sets of eight repetitions at a load of 8RM. Between sets and exercises a 2–3 min rest	FSS, MFI-20, Major depression Inventory, SF-36, knee MVC scores and functional capacity scores	Fatigue Severity Scores and general fatigue scores of MFI-20 improved significantly in Group 1 compared to the control group ($p<0.05$). The beneficial effects were maintained at follow-up	Improvement in mood and QOL. The beneficial effect was maintained at follow-up.

N-number of subjects; RCT-Randomized Controlled trial; FSS- Fatigue Severity Scale; MFIS- Modified Fatigue Impact Scale; EDSS-Expanded Disability Status Scale; MSFC- MS Functional Composite

Table 4: Effect of Resistance Exercises on Fatigue in Individuals with MS.

initially the participants felt the need for rest; however, closer to the end of the program the participants felt more energized and revitalized and also had less tiredness. Overall it was reported that disability and mobility improved with the aerobic training [57] (Table 5). The effects of aerobic training in resolving fatigue was also studied in a group of individuals with MS (N=112) randomly divided into the aerobic training group (1), neurophysiologically based neuro-physiotherapy group (2), group with a combined therapy (3) (combination of the aerobic training and neurophysiologically based neurophysiotherapy used in treatment of groups 1 and 2) and the control group (4) in which the participants did not change their present habits during the duration of the experiment. Of the four groups, the neurologically based neurophysiotherapy (group 1) showed the greatest impact on regulating depression, impairment, disability, QoL and spirometric and spiro-ergometric parameters. At the same time groups 1, 2 and 3 showed greater improvements in fatigue scores as compared to the control group [58].

It was also demonstrated that aerobic exercise performed using elliptical training machines can help reduce fatigue associated with MS. Implementing elliptical exercise for patients with MS also resulted in significant improvements in quality of life and physical function [59].

Aquatic therapy

Aquatic therapy exercises commonly include pool therapy, hydrotherapy or balneotherapy. Hydrotherapy is frequently provided to patients with painful neurological or musculoskeletal conditions. The positive effects of aquatic therapy are associated with the effects warm water has on the body: it increases blood flow, enhances muscle relaxation and helps in blocking nociceptors by stimulating mechanoreceptors. In addition, the hydrostatic effects help to reduce pain by reducing peripheral edema and sympathetic nervous system activity [39]. It is also important to note the properties of buoyancy and viscosity of water facilitate physical activity, which can aid those with physical weakness [52].

Several studies have focused on the role of aquatic therapy in combating fatigue in individuals with MS. Among them, a randomized controlled trial examined the effectiveness of aquatic exercise on fatigue and health related quality of life in women with MS. Eight-weeks of aquatic training led to improvements in fatigue and HRQOL in the participating individuals with MS as compared with the control group [52] (Table 6).

Another interesting study involved a ten-week aquatic exercise

Reference & Year	N	Study Design	Inclusion Criteria	Duration of Intervention	Study Groups	Intervention	Outcome Measures used	Effect of Interventions on Fatigue	Comments
Aerobic Exercises									
Kileff and Ashburn 2005 [57]	6	Comparitive pilot study	EDSS between 4 and 6 Ambulation with or without aid	2 times per week for 2 weeks	Pre and post intervention	30 min of static bike exercise at the maximum level of exertion	10 meter and 6 MWT, functional reach test, the Gulick and Guys Neurological disability scale, Fatigue severity scale, Modified Ashworth's scale.	Reduction in fatigue although not statistically significant.	Significant improvement on the GNDS and 6MWT. Overall mobility improved and disability reduced
Rasova et al. 2006 [58]	95	RCT	EDSS 0-6.5. ability to walk 20m using crutches	3 times per week for 4 weeks	Group 1: Aerobic training (n=36) Group 2: Neurophysiologically based neuro-physiotherapy (n=24) Group 3: Combination of the aerobic training and neurophysiologically based neurophysiotherpy (n=19) Group 4: Control: (n=16)	Neurologically based physiotherapy, 30 min cycling and combined therapy of these two.	EDSS, Barthel Index, Environment Status Scale, MS Quality of Life, Modified Fatigue Impact Scale, Beck Depression Inventory Score, spirometry and bicycle ergometeric measurements.	Significant reduction in fatigue in groups 1, 2 and 3	Pulmonary ventilation, fatigue, depression were significantly improved in groups 1, 2 and 3. No changes in Group 4
Huisinga et al. 2011 [59]	26	Comparative	EDSS score between 1.0 to 6.0 and ability to walk 25 feet	6 weeks	Pre and post intervention	30 min elliptical exercise	FSS, Modified MFIS, and the Short Form Health Survey (SF-36)	Significant decrease in the fatigue scores on the FSS and the MFIS	Increased SF-36 scores in the physical function, emotional role, energy subscale, social function and general health subscales.

N-number of subjects; RCT-Randomized Controlled trial; FSS-Fatigue Severity Scale; MFIS-Modified Fatigue Impact Scale; EDSS-Expanded Disability Status Scale; MSFC-MS Functional Composite, GNDS-Gulick and Guys Neurological disability scale, 6MWT-Six minute walking tests

Table 5: Effect of Aerobic Exercises on Fatigue in individuals with MS.

Reference & Year	N	Study Design	Inclusion Criteria	Duration of Intervention	Study groups	Intervention	Outcome Measures used	Effect of Interventions on Fatigue	Comments
Aquatic Exercises									
Kargarfard et al. 2012 [52]	21	RCT	EDSS 3.5, ability to participate in regular exercise sessions	8 weeks with a follow-up at 4 and 8 weeks	Group 1: Exercise (n=10) Group 2: Control (n=11)	Aquatic training focused on joint mobility, flexor and extensor muscle strength, balance movements, posture, functional activities, and intermittent walking	MFIS and QOL-54	Significant improvement in fatigue after 4 and 8 weeks	Significant improvements in subscores of HRQOL
Gehlsen et al. 1984 [60]	10	Comparative	Ability to ambulate, remissive state.	10 week	Pre and post intervention assesments	Freestyle swimming and shallow water calisthenic exercises	Upper and lower extremity muscle torque, force, fatigue, work and power obtained using the Cybex II isokinectic dynamometer and a biokinetic swim bench Muscle fatigue was calculated from the total work data	Improvement in the fatigue of the lower extremities	Positive changes in strength, fatigue, work and power
Pariser et al. 2006 [61]	2	Comparative	EDSS 2.5-3	2 times a week for 8 weeks	Pre and post interventions assesments	10 min of warm-up, 30 min of aerobic exercises in water-Aqua aerobics and a 20 min cool down period.	Maximal graded exercise test, the lactate threshold (from blood samples) and fatigue using the FSS	Reduction in fatigue for one participant. No improvements in fatigue levels for the second participat	
Castro-Sanchez et al. 2012 [39]	73	RCT	EDSS score >7.5, Visual Analogue Scale pain score (VAS) >4	2 times for 20 weeks	Group 1: Tai-Chi exercise (n=36) Group 2: Relaxation (n=37)	40 sessions of Tai Chi in swimming pool	McGill pain Questionnaire, Roland Morris Disability Questionnaire, Fatigue Severity scale, Becks depression Inventory and Barthel Index	Significant reduction of fatigue on the MFIS and FSS	Significant r eduction in pain, VAS for spasm, MS impact scale-29, Beck Depression Inventory II, Barthel Index.

N-Number of subjects; RCT-Randomized Controlled trial; FSS-Fatigue Severity Scale; MFIS-Modified Fatigue Impact Scale; EDSS-Expanded Disability Status Scale; MSFC-MS Functional Composite, GNDS-Gulick and Guys Neurological disability scale, 6MWT-Six minute walking tests

Table 6: Effect of Aquatic Exercises on Fatigue in Individuals with MS.

program including strength and endurance training in form of freestyle swimming and shallow water callisthenic exercises [60]. In that study, the temperature was maintained within 25-27.5 degree Celsius and the progression of exercises was based on the assessment of sub-maximal heart rate, subjective feelings of fatigue and also by monitoring heart rate responses during training in the study participants. The outcome of the study included positive changes in muscular strength, fatigue, work and power as a result of the aquatic program [60].

The effects of an aquatic program on fatigue in MS was investigated in another study involving 2 females diagnosed with MS more than 10 years prior to the study [61] who performed aquatic exercises for 30 minutes twice a week for 8 weeks. While the effect of aquatic exercises on fatigue was not the same between the two subjects, the authors suggested that aqua therapy/hydrotherapy may help individuals with MS in reducing the symptoms related to fatigue [61].

Importantly, participation in biweekly Tai Chi exercises performed in water (Ai Chi) for five months was associated with significant improvements in the symptoms of fatigue, spasms, depression, quality of life and reduced pain levels in participants with MS as compared to the control group, which participated in the relaxation activities [39]. What is noticeable is that the study also showed that the positive effects of the Tai Chi aquatic exercise program lasted for 4 to 10 weeks after the end of therapy. Based on the outcome of the study, it was suggested that aquatic Tai Chi can be a valuable activity in helping individuals with MS cope with fatigue as well as in resolve pain and depression [39].

Discussion

The review of the available literature suggests that there are therapies that can help in resolving or minimizing fatigue in individuals with MS. Among these therapies are techniques based on utilizing the mind and body approach and exercise activities. It is important to consider that not all the reviewed papers reported improvements in fatigue after intervention, and there was no single study with fatigue as the only outcome measure. As such, when reviewing the literature the focus was on the improvement in a number of parameters in addition to fatigue. Among them are depression, QoL, mood and balance, as well as cognitive function.

The outcomes of the studies involving the mind and body approach described in this review have shown a positive trend towards improvements of fatigue. A number of studies reported that practicing Yoga, Tai Chi, and participation in neurocognitive and energy conservation courses can reduce the level of fatigue in individuals with MS. On average, the mind and body therapy interventions lasted 6-12 weeks, some lasted for even longer periods, suggesting that the duration of practicing a particular activity might be a factor playing a role in the reduction of fatigue. Performing yoga for 48 weeks was associated with reductions in fatigue [23], while 10 weeks of practicing yoga was not [26]. As such, the selection of the duration of practicing yoga should be tailored to the needs of a particular patient allowing the participant to tolerate the activity well.

The reviewed literature on the effects of Tai Chi suggests that its role in resolving fatigue may be two-fold. It was shown that practicing Tai Chi was associated with improvements in fatigue but also led to improvements in balance in individuals with MS [4]. As such, it was argued that as a result of improvements in balance, there could be improved mobility, and it may be easier for the individual to cope with fatigue [62].

The literature provides evidence that the motor imagery (that is a part of the Neurocognitive rehabilitation) is essential in the management of fatigue. Motor imagery utilizes the patient's own strength in order to overcome the weakness, which in this case is the fatigue associated with MS. The reviewed papers, that are based on the use of the neurocognitive strategies, have shown encouraging results in form of improvement in the ability to deal with fatigue in the individuals with MS.

Another important approach in reducing fatigue in individuals with MS is based on the use of the energy conservation techniques. Thus far, the outcomes of the reviewed papers are encouraging as they provide support for the importance of learning and using the energy conservation approaches in the management of fatigue. Overall, mind and body approaches were found to be beneficial in minimizing the effect of fatigue in individuals with MS. In 2002 about 62% of people in the United States used Complementary and Alternative Medicine (CAM), with mind–body medicine being the most commonly used CAM form [63]. Thus, one can expect that the use of the mind and body approach to resolve the effects of fatigue in individuals with MS will increase in the future.

The reviewed literature suggests that exercise activity is an important element in attempts to resolve fatigue in individuals with MS. In addition, exercises can be used to address muscle weakness, which is a common and contributing factor in the exacerbations of the disease. As such, exercise activity can positively affect the lives of individuals with MS. Based on the reviewed literature, progressive resistance exercises at community centers or gyms in the form of strengthening exercises focused on minimizing the effect of fatigue could be a suggested activity for the people with MS who have a mild to moderate level of disability.

Aerobic exercise has also shown notable improvements in reducing the fatigue in individuals with MS. Aerobic exercise training for 2-4 weeks may be beneficial in reducing fatigue and improving the mobility as well. Future research is needed to provide additional data on the efficacy of the combination of the resistance and aerobic exercises in reducing fatigue in people with MS.

Resistance and endurance training in the form of hydrotherapy performed in water may offer additional benefits to individuals with MS. The effect of buoyancy helps patients with muscle weakness and spasticity to participate in exercise activity. The literature also suggests that aquatic therapy helps to increase the endurance as well as the strength of muscles. Positive results can be expected from the aquatic therapy for individuals with MS, and hydrotherapy can be considered as one more alternative approach in dealing with the fatigue associated with MS.

It is important to note that a number of therapies and approaches that potentially can help individuals with MS to address fatigue were not included in the review because it was difficult to classify them to either mind or body or exercise activities sections. Among them are approaches that focused on improving balance [64,65]. Indeed, some researches argued that fatigue could be resolved as a result of exercise activities focused on improvement of balance in individuals with MS. For example, it was suggested that when balance is improved, less energy will be spent on maintaining balance to perform various activities, which in turn would help in dealing with fatigue [62]. Moreover, interventions like Hippotherapy [66], elliptical exercise [59], core stability training [67] and vestibular training [68] have also shown to help in the improvement of balance. For example, core stability exercise help the body to better cope with the perturbations

during activities like stepping, lifting, walking, etc. [67]. Such approaches might provide an added benefit to alleviate the effects of fatigue in individuals with MS and could be beneficial in resolving fatigue. However, only a few studies have focused on establishing the relationship between the improvements in balance and the reduction in the fatigue in individuals with MS [62]. As such, future research should be focused on investigation of the existence of such a relationship.

Conclusion

The reviewed literature suggests that mind and body interventions such as Yoga, Tai Chi, Neurocognitive exercises, and energy conservation techniques along with approaches involving endurance training, resistance training and aquatic therapy can help individuals with MS in resolving fatigue.

Further research is necessary to determine whether each individual therapy or a combination of therapies can be beneficial in resolving fatigue in patients with MS.

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