Exercise in the management of persons with multiple sclerosis

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***Abstract*:** For decades, persons with multiple sclerosis (MS) were counseled to avoid excessive physical activity and exercise because of concerns about worsening disease activity. Recent studies indicate that, not only can those with MS tolerate physical exercise, but that it is helpful in managing symptoms, preventing complications and comorbidities, and may possibly have neuroprotective actions. This article reviews previous studies on the effects of different exercise protocols in people with MS, and provides summaries of suggested exercise regimens that may be appropriate and beneficial for this patient population.

Keywords: exercise, aerobic, resistance, co-morbidity, neuroprotection

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Introduction

As recently as a few decades ago, conventional wisdom held that persons with multiple sclerosis (MS) should avoid strenuous physical activity because of concerns that it might worsen their neurological status. This may have stemmed from the observation that most persons with MS may temporarily have exaggerated symptoms when they become overheated, e.g. as might happen with vigorous physical exertion. It is now becoming clear that this advice for those with MS not to be physically active was not only incorrect, but likely had potentially harmful consequences in terms of promoting deconditioning and contributing to comorbidities such as obesity, metabolic syndrome and osteoporosis, to name just a few.

Fortunately for people with MS and the healthcare professionals who treat them, there are now abundant data that demonstrate that physical activity is not only safe and well-tolerated for persons with MS, and has the same health benefits as it does for the general population, but additionally may be of value in alleviating some symptoms, preventing complications and possibly being neuroprotective. Obesity has been implicated as a risk factor for developing MS in adolescent girls [Langer-Gould *et al.* 2013] and other data suggest that those with MS with vascular comorbidities, such as hypertension and diabetes, have more disability and worse prognosis [Marrie and Harwell, 2013]. A recent review of 26 randomized, controlled trials (RCTs) of exercise training in persons with MS found a slightly decreased risk of relapse in the exercise group *versus* control (6.3% *versus* 4.6%)and no increase in risk for adverse events compared with the risk of adverse events for exercise training in a non-MS population [Pilutti *et al.* 2014]. Thus exercise may actually impact disease course in persons at risk for MS and after the disease develops, i.e. it might be potentially considered as a disease modifying therapy.

Unfortunately, persons with MS have been shown to be less physically active than healthy controls [Motl, 2014]. A survey of 417 persons with MS identified fatigue, impairment and lack of time as the top three barriers to exercise [Asano *et al.* 2013].

This paper reviews the data about exercise in the animal model of MS, experimental autoimmune encephalomyelitis (EAE), and then summarizes what has been observed about the effects of physical exercise on specific MS symptoms and impairments. Emerging data about the possible neuroprotective/neurorestorative properties of exercise are explored. Finally, current recommendations for appropriate exercise regimens for persons with MS are discussed.

The definition of exercise training is that of taken from Motl and Pilutti who defined it as ‘planned, structured and repetitive physical activity undertaken over a prolonged period to maintain or improve physical fitness and functional capacity’ [Motl and Pilutti, 2012]. This is to distinguish it from physical therapy, which may be defined as a structured set of exercises and strategies designed to overcome a specific deficit. The benefits of physical therapy for persons with MS are outside the scope of this review.

Exercise and EAE

EAE is the most studied animal model for MS and can be actively or passively induced in several rodent species. Disease severity is generally graded on a scale from 0 to 5, where '0' is asymptomatic, grades 1–4 indicate increasing degrees of motor deficit, and 5 is quadriplegic or moribund [Klaren *et al.* 2014]. The first study examining the effect of exercise in EAE used a forced running paradigm in rats beginning 1 day after disease induction. The exercised rats showed a significant delay in onset and decreased severity of disease compared with control (sedentary) rats [Le Page *et al.* 1994]. A follow-up study confirmed that exercise appeared to have maximal benefit when performed just after disease induction at high intensity, compared with exercise initiated before disease induction or after induction at variable speeds [Le Page *et al.* 1996].

More recent studies in murine EAE models have variably demonstrated benefits of exercise. Rossi and colleagues employed a voluntary exercise paradigm in mice and reported lower disease severity in both acute and chronic phases of EAE in mice with access to a running wheel, compared with mice without wheel access [Rossi *et al.* 2009]. Additionally, the exercised mice had less neural damage as assessed by electrophysiological responses, and increased dendritic spine density compared with controls. Another study used swimming exercise in mice as the exercise paradigm, where the exercised mice were made to swim 30 minutes/day for 5 days/week for 6 weeks. A control group of mice was placed in the water on a platform for the same time period. EAE was induced during the fifth week of training in both exercised and sedentary mice; a control group in each condition received sham injections. The EAE plus exercise mice showed decreased disease severity compared with controls [Bernardes *et al.* 2013]. The exercised mice showed increases in brain-derived neurotrophic factor (BDNF) and decreased demyelination compared with nonexercised mice with EAE, but cytokine patterns were not consistently different between the groups. Finally, a paradigm using forced treadmill walking in rats that were exercised for 10 days after induction of chronic EAE did not show any difference in clinical severity or levels of BDNF and tumor necrosis factor-α (TNF-α) between exercised and control rats, although the clinical disability score in both groups (1.0 = tail weakness) was low [Patel and White, 2013].

While the majority of this small number of studies suggest a beneficial effect of exercise on EAE, the study populations, types of exercise and timing of exercise all vary, and further research is needed in this area. For a complete review see the article by Klaren and colleagues [Klaren *et al.* 2014].

Specific impairments

This section presents a review of studies of the effects of exercise on impairments specific to those with MS; control groups in these studies being those persons with MS who were randomized to a nonintervention group, e.g. waiting list, usual care or other control intervention.

Muscle strength/mobility/spasticity

Numerous studies have demonstrated that exercise training can improve muscle strength in persons with MS. Protocols have included progressive resistance training (PRT), aerobic exercise (AE), combined AE and PRT, and other activities such as swimming and robotic-assisted treadmill training. Despite different subject populations and protocols, studies have consistently reported improvements in muscle strength after training. A review of PRT [Kjolhede *et al.* 2012] examined results from six RCTs of PRT and six noncontrolled trials. The RCTs included subjects with expanded disability status scale (EDSS) scores ranging from 1.0 to 6.5, and duration and intensities of training ranging from 2 to 5 sessions/week over 3–20 weeks. Training modalities included free weights, resistance bands or weight machines.

Reviews of aerobic and other training modalities also report improvements in muscle strength. The seminal study of Petajan and colleagues was one of the first to report improvements in muscle strength in persons with MS after they were randomized to a protocol of arm and leg cycling 3 times per week for 15 weeks *versus* usual care [Petajan *et al.* 1996]. Improvement in muscle strength has also been reported with robotic-assisted treadmill training [Beer *et al.* 2008], swimming [Gehlsen *et al.* 1984] and a combined AE plus PRT regimen [Konecny *et al.* 2010]. Sá has provided a comprehensive review of the physical (musculoskeletal) effects of exercise training in persons with MS [Sá, 2013].

Muscle strength has been reported to be an important determinant of walking speed in persons with MS [Thoumie *et al.* 2005]. The effects of AE and PRT on walking speed in RCTs have been somewhat less consistent than the effects on muscle strength noted above. At least one RCT of PRT [Dalgas *et al.* 2009] and one RCT of treadmill walking (Van den Berg *et al.* 2006] have reported improvement in walking speed; non controlled trials have also reported improvements [Motl and Pilutti, 2012].

A few studies have reported positive effects of exercise on reducing spasticity in persons with MS. These have included cycling [Sosoff *et al.* 2009], a group exercise intervention [Tarakci *et al.* 2013] and locomotor training [Giesser *et al.* 2007].

Fatigue

Fatigue is the most common symptom reported by person with MS, with an incidence of up to 90% in some studies. It is not solely a function of physical disability and may be the single most disabling symptom in an otherwise neurologically intact individual. Usual treatment measures include pharmacologic agents and energy conservation methods.

A review of the effects of exercise on fatigue in persons with MS has yielded somewhat heterogeneous results, with some studies demonstrating a benefit in improving fatigue, and other studies failing to show improvement. Improvement in fatigue has been reported in some trials of aerobic exercise [Petajan *et al.*1996; Rampello *et al.* 2007; Sabapathy *et al.* 2011], PRT [Dalgas *et al.* 2010], AE and PRT combined [Konecny *et al.* 2010] and other forms of activity such as sport (volleyball) [McCullagh *et al.* 2008], yoga [Oken *et al.* 2004] or aquatic exercise [Sutherland *et al.* 2001], to name a few. A meta-analysis of RCTs examining the effects of exercise training on fatigue found an overall small but significant benefit, with an effect size of 0.45 [Pilutti *et al.* 2013].

Importantly, no study has demonstrated a significant worsening of fatigue with any type of exercise, thus providing important reassurance for patients that they should be able to exercise safely without worsening their condition, other than possible temporary effects from overheating.

Mood

Depression may affect up to 50% of the MS population [Sadovnick *et al.* 1996] and can significantly impact other symptoms such as fatigue and pain, as well as negatively affecting cognition and quality of life. A recent Cochrane review found a small but significant effect of exercise on persons with depression (without MS) compared with waiting list or placebo [Cooney *et al.* 2013]. Petajan and colleagues performed one of the first studies to demonstrate that exercise could produce improvements in mood in person with MS [Petajan *et al.* 1996]. A recent review of the effects of exercise on depression in persons with MS reported heterogeneous results, with several studies using aerobic and PRT reporting positive effects on depression, and other trials failing to note improvement [Feinstein *et al.* 2013]. The authors note that none of these studies had depression as a primary outcome measure or used a clinician-based assessment of depression as an outcome measure, and suggest that further clarity is needed in this area. A more recent review of 13 RCTs of the effect of exercise on depressive symptoms in people with MS reported an effect size of 0.36 [Ensari *et al.* 2014].

Quality of life

Health-related quality of life (HRQOL) has been reported to be reduced in persons with MS compared with those without MS and those with other chronic medical conditions [Benito-Leon *et al.* 2003]. A meta-analysis of studies of the effects of exercise on HRQOL in persons with MS concluded that, despite reports of individual studies reporting improved HRQOL with exercise, both with aerobic [Petajan *et al.* 1996; Romberg *et al.* 2004], PRT [Dalgas *et al.* 2010] and combined protocols [Dalgas *et al.* 2010], overall there was insufficient consistent evidence to prove definitively that exercise improved HRQOL in this patient population, as other studies of exercise did not show HRQOL improvement [Latimer-Cheung *et al.* 2013b].

Cognition

Exercise, primarily aerobic, has been reported to improve cognitive function in several patient populations, including Alzheimer's disease (AD), elderly people at risk for cognitive impairment and healthy older adults [Voss *et al.* 2013; Smith *et al.* 2010]. The literature on the effects of exercise in cognition in persons with MS is scant, although the animal literature consistently reports positive effects of exercise upon cognition [Van Praag *et al.* 2005; Cotman *et al.* 2007]. Improved physical fitness has been reported to correlate with improved cognitive function in persons with MS [Motl *et al.* 2011; Beier *et al.* 2014] and that cardiorespiratory fitness in persons with MS predicts neuronal plasticity [Prakash and Snook, 2007] and increased gray matter volume, better white matter integrity and improved performance on test of information processing speed [Prakash *et al.* 2010].

An early study employing a light intensity aerobic regimen or yoga failed to show improvement in performance on neurophysiologic tests [Oken, 2004]. However, a more recent RCT of an aerobic exercise intervention in persons with MS reported improved cognitive function in several neuropsychological domains in subjects who received the exercise intervention, compared with a waiting list control group [Briken *et al.* 2014]. A study using a computer/internet based intervention to increase physical activity behavior demonstrated a clinically significant increase in the Symbol Digit Modalities Test (SDMT) in a subset of subjects with mild disability at the end of the intervention while there was minimal change in this metric in a waiting list control group [Sandroff *et al.* 2014].

Neuroprotective effects

Exercise has been shown to ameliorate the effects of trauma or disease to the central nervous system (CNS) in animal models of stroke [Hayes *et al.* 2008], spinal cord injury [Gomez-Pinilla *et al.* 2012], AD [Voss *et al.* 2013] and MS [Voss *et al.* 2013]. There is some evidence for neuroprotective effects of exercise in humans with MS, with a few trials of aerobic or aerobic plus resistance exercise training producing decreases in anti-inflammatory cytokines compared with non-exercised controls [Motl and Pilutti, 2012]. There is substantial evidence for increases in neurotrophins in response to exercise in the animal literature [Cotman *et al.* 2007]. One trial of aerobic exercise in persons with MS reported a transient increase in BDNF during an aerobic exercise regimen [Castellano and White, 2008]; another trial did not report significant increase in BDNF after exercise [Schultz *et al.* 2004]. More recently a trial comparing aquatic *versus* land exercise training in persons with MS reported that increases in BDNF were seen in the aquatic trained group [Bansi *et al.* 2013].

Exercise has been shown to increase synaptic density and growth in the hippocampus in the animal model of MS [Rossi *et al.* 2009]. One study in two people with MS reported a substantial increase in hippocampal volume in the subject randomized to an aerobic exercise program compared with a nonaerobic trained control [Leavitt *et al.* 2014].

Given that the primary mechanism of nerve damage in relapsing-remitting MS is inflammatory, if exercise has an anti-inflammatory effect through a combination of mechanisms (e.g. reducing inflammatory cytokines and reducing adipose tissue, which itself has been shown to produce inflammatory cytokines [Chan *et al.* 2013]), this would be a disease-modifying modality that appears to be well-tolerated by persons with MS and also cost effective. A review of exercise intervention studies that have used clinical outcome measures of disease progression or disability concluded that there are currently no data to date to establish a disease-modifying effect of exercise, but state that future studies and improved methodologies are necessary to answer this question [Dalgas and Stenager, 2012].

Recommendations

One of the difficulties repeatedly identified in the reviews and meta-analyses cited above is the heterogeneity of methodologies employed. A recent review suggests the following outcome measures for use in exercise studies in MS [Paul *et al.* 2014]:

- Fatigue: Modified Fatigue Impact Scale (MFIS) [Fisk *et al.* 1994] or Fatigue Severity Scale (FSS) [Krupp *et al.* 1989].
- Six Minute Walk Test (6MWT) for exercise tolerance [Goldman *et al.* 2008].
- Timed Up and Go (TUG) for muscle function and mobility [Podsiadlo and Richardson, 1991].
- MS Impact Scale 29 (MSIS-29) or MS Quality of Life 54 (MSQOL 54) [Vickrey *et al.* 1995] for QOL.
- Body mass index (BMI) or waist hip ratio for assessment of health risks associated with obesity.

One study has reported that a change of approximately 800 steps/day is the minimal clinically important difference (MCID) in ambulatory persons with MS, suggesting that this may be a useful metric for studies looking at the effects of exercise on ambulation [Motl *et al.* 2013].

Table 1. Published suggested exercise guidelines for persons with MS.

Study	Aerobic	Resistance	Aerobic activity	Resistance activities
Dalgas *et al.* [2008]	10–40 min 2–3 times a week	8–15 repetitions/set, 3–4 sets per exercise, 2 days/week	Cycling, arm ergometry, treadmill walking, aquatics	Not specified
Latimer-Cheung *et al.* [2013a]	30 min twice a week	10–15 repetitions/set, 2 sets per exercise, 2 days/week	Cycling, arm ergometry, elliptical trainer, aquatic exercise	Weight machines, free weights, elastic resistance bands

Because of the heterogeneity of methods in trials of exercise as a therapeutic modality, currently there are few standard guidelines for the optimal type of exercise that should be prescribed for persons with MS, although obviously there will be individual needs that must be taken in to account. These would include level of disability, cognitive status, fatigue, heat sensitivity or other subject-specific impairments.

The analyses of studies indicate that ideally both aerobic and resistance exercises may benefit persons with MS. Although Petajan and colleagues did not make formal recommendations *per se* in their publication, their protocol was 40 minutes of aerobic training 3 times per week. They noted that the social aspect of exercising in small groups, as opposed to training alone, appeared to be important in promoting adherence to exercise [Petajan *et al.* 1996]. Dalgas and colleagues suggested a regimen of 10–40 minutes/session of aerobic activity, performed at 60–80% of maximal heart rate. Suggestions for a combined regimen are 2 days/week each of aerobic and resistance training, with 24–48 hours rest between training sessions [Dalgas *et al.* 2008] (Table 1).

Similar recommendations for exercise for persons with MS are those of Latimer-Cheung and colleagues who published guidelines based on their review of published studies of different exercise regimens on various symptoms and impairments seen in persons with MS [Latimer-Cheung *et al.* 2013b]. Their recommendations are directed at adults with MS with 'mild to moderate' disability, and also suggest combined aerobic and resistance exercises [Latimer-Cheung *et al.* 2013a] (Table 1).

Persons with lower extremity weakness can concentrate on upper body exercises (arm ergometry, resistance) or aquatic exercise. Persons with marked fatigue or deconditioning may have to begin training at lower intensities and durations, and may take longer to reach maximal intensity and duration of exercise than someone who is more fit at baseline. All persons with MS should employ cooling strategies during exercise so as to mitigate increases in core body temperature which could temporarily aggravate symptoms.

An emerging concept is that lifestyle physical activity is an important and quantifiable adjunct to prescribed exercise training [Motl, 2014]. Persons with MS may increase physical activity though sports, household chores, occupation or transportation. Tracking may be accomplished by activity logs and inexpensive personal accelerometer devices.

Conclusion

Persons with MS are less physically active than the general population. In addition to preventing potential complications of being sedentary, such as deconditioning, osteoporosis, obesity or vascular comorbidities, physical exercise can play an important role in managing specific symptoms in persons with MS and may possibly be neuroprotective. Research in this area has suffered from heterogeneity of patient population, exercise regimen and outcome measures. Further information is needed to determine the optimal exercise regimen for persons with MS, and which specific exercise modalities may benefit specific symptoms and impairments. In the meantime, healthcare providers should encourage physical activity for their patients with MS, as it has been demonstrated to be safe and well tolerated.

Conflict of interest statement

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