Effective Rehabilitation Methods in Patients with Multiple Sclerosis

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Abstract

The role of rehabilitation in managing symptoms of multiple sclerosis (MS) and promoting functional recovery has grown exponentially over the past 12 years. Evidence now supports strength and aerobic training for individuals with mild or moderate disease. An emerging body of evidence suggests that exercise may play a role in the production of brain-derived neurotrophic factor in individuals with MS, and the combination of pharmacological management and rehabilitation may produce better outcomes than one therapeutic intervention alone. Rehabilitation and exercise should be a major focus in the comprehensive management of MS.

Keywords

Rehabilitation, multiple sclerosis, aerobic exercise, strength training, treadmill training, brain-derived neurotrophic factor, symptom management

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Multiple sclerosis (MS), which affects an estimated 400,000 people in the US, is a demyelinating disease with a variable degree of injury to axons in the brain, spinal cord, and optic nerve.[1] A variety of symptoms associated with MS—such as weakness, spasticity, balance problems, and ataxia—affect functional mobility and activities of daily living. Studies have also suggested that physical inactivity over a three- to five-year period can produce a worsening of symptoms, independent of depression, Expanded Disability Status Scale (EDSS) score, and disease course.[2] Symptom management in MS has emphasized medical management, but in recent years rehabilitation has been added as an adjunctive treatment.

Research examining rehabilitation in MS has progressed rapidly within the past 10 years, with an emerging body of evidence to suggest that exercise programs have a beneficial effect on both disease symptoms and the general fitness of people with MS who are ambulatory.[3] Early research reported by Gehlsen et al.,[4] Chen et al.,[5] Brar et al.,[6] and Petajan et al.[7] examined the benefits of aquatic exercise, stretching exercise, and the use of baclofen for spasticity, muscle force production in the lower extremities, and physical and psychological changes, respectively.

In the past 15 years research has focused more on the type of exercise that may have an effect on MS symptoms, as well as the role of neurological rehabilitation in functional recovery. For many patients, medications to manage the disease and symptoms, as well as aggressive rehabilitation, have led to advances in functional recovery.

Aerobic and Strength Training

The effectiveness of exercise in individuals with MS was first investigated by Petajan et al. in 1996.[7] Fifty-four patients with MS were randomly assigned to exercise or non-exercise groups. Subjects in the experimental group exercised for 40 minutes three times per week for 15 weeks. The exercise consisted of combined arm and leg ergometry. Compared with baseline measures, the exercise group demonstrated significant increases in maximal oxygen consumption (VO_2 max) and upper- and lower-extremity strength, and significant decreases in skinfold, triglyceride, and very-low-density lipoprotein (VLDL) measurements. Depression and anger scores were also significantly reduced at weeks five and 10, and fatigue was reduced at week 10. Compared with the non-exercise subjects, exercise training resulted in improved fitness and had a positive impact on factors related to quality of life.

In 2004, White et al.[8] conducted a small study (n=8) examining progressive resistive exercise in people with MS. White reported a significant change ($p<0.05$) after the eight-week program in knee extension (7.4%), plantarflexion (52%), and stepping performance (8.7%). In addition, self-report by the subjects reflected a decrease in fatigue. This small study suggested that people with MS are capable of making positive adaptations to resistance training that may be associated with improved ambulation and decreased fatigue. Specific gait measures were not analyzed in the study by White et al.

Another eight-week progressive resistance training program was conducted by Guiterrez in 2005.[9] In this specific study, the main outcome measures were kinematic gait parameters, including knee range of motion, duration of stance, swing, and double-support phases in seconds and percentage of time in each gait phase. Isometric strength, three-minute stepping, fatigue, and self-reported disability were also measured. After two months of resistance training, there were significant increases ($p<0.05$) in stride time and step length, and isometric leg strength improved ($p<0.05$) in two of the four muscle groups tested. Subject self-report of fatigue indices also decreased ($p=0.04$). The authors concluded that resistance training may be an effective intervention strategy for improving walking in moderately disabled persons with MS.

Bjarnadottir[10] conducted a randomized controlled trial (RCT) to determine the effect of aerobic and strength exercise on physical fitness and quality of life in people with mild MS (EDSS <4). Sixteen outpatients, 18–50 years of age, completed the study (experimental group n=6). The experimental group exercised three times a week for five weeks, while the control group maintained their usual exercise habits. The mean change in workload was 0.34W/kg (95% confidence interval [CI] 0.09–0.58), the mean change in VO_2 peak was 4.54ml/kg/minute (95% CI 1.65–7.44), and the mean change in anaerobic threshold was 0.32l/minute (95% CI 0.08–0.57). The authors concluded that brief, moderate aerobic exercise improves physical fitness in individuals with mild MS.

Treadmill Training

In 2006, van den Berg[11] conducted a four-week aerobic treadmill training program with 16 subjects diagnosed with MS. The study design had an immediate exercise group and a delayed exercise group. The authors reported a significant difference in walking endurance between the two groups and a decrease in 10m walk time for both groups, with a significant change in the immediate exercise group ($p<0.05$). The authors concluded that individuals with MS can benefit from aerobic treadmill training, with potential for walking speed and endurance to improve following training. There was no increase in fatigue reported by the subjects. Benedetti[12] reported a similar finding with three subjects followed in a case study design who completed a four-week aerobic treadmill exercise program. The authors reported that aerobic treadmill training is feasible and safe and may improve early anomalies of posture and gait in mildly impaired individuals.

Occupational Therapy

One of the primary symptoms reported by individuals with MS is fatigue.[13] In 2007, Mathiowetz et al.[14] published their research findings examining the one-year post-course effects of a six-week community-based energy-conservation course taught to individuals with MS. The results showed that the beneficial effects were maintained one year post-course compared with immediately post-course. In addition, there were significant improvements in all three subscales of the Fatigue Impact Scale and in four subscales of the Short Form-36 Health Survey (SF-36) at one year post-course compared with pre-course. These results provide strong evidence that the beneficial effects of the energy-conservation course taught by occupational therapists, which were maintained up to one year post-course, can have an impact on a major symptom of MS.

Cognitive impairment is another common symptom for people with MS. A study by Gentry et al.[15] evaluated the effects of an occupational therapy training protocol using personal digital assistants (PDAs) as assistive technology to help with cognitive impairment related to MS. Twenty participants were trained to use PDAs by an occupational therapist, and assessments of functional performance were taken at the start of an eight-week pre-treatment period and at the end of training. The authors reported that the participants demonstrated the ability to learn how to use basic PDA functions and retain learning for at least eight weeks. In addition, functional performance increased significantly with PDA use, and this gain was maintained at eight-week follow-up.

Stretching Exercise and Baclofen (Lioresil) for Spasticity

Evidence supporting the use of therapeutic exercise focusing on stretching spastic muscles is inconclusive.[16] There is some positive evidence supporting the immediate effects of one stretching session; however, it remains unclear how long these effects last and if there are any long-term consequences.[16] One study that does merit further research is that by Motl et al.,[17] who examined the effect of a single bout of unloaded leg cycling on the soleus H-reflex and modified Ashworth scale (MAS). Twenty-seven individuals with MS who had spasticity of the leg muscles but were not taking antispastic medications participated in the study. The soleus H-reflex and MAS data were collected before and 10, 30, and 60 minutes after 20 minutes of unloaded leg cycling. The 20-minute leg cycling program resulted in immediate and prolonged reductions in the soleus H-reflex and MAS scores compared with a control condition. This particular intervention requires further investigation to examine blood flow to the spastic muscles and the length of time needed to produce a prolonged effect.

Baclofen (Lioresil) is an antispastic medication frequently prescribed for individuals with spasticity resulting from an upper motor neuron lesion. The pharmacological action of baclofen is to enhance the activity of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter. There have been limited studies examining its effect in MS, but in 1991 Brar et al.[6] reported that treatment with baclofen alone significantly improved moderate quadriceps spasticity, as measured by Cybex flexion scores, in individuals with MS. The test used in the Brar study (Cybex flexion score) is not necessarily a valid or reliable measure of spasticity; however, clinical observation suggests that oral baclofen or baclofen delivered intrathecally can produce changes in spasticity that may promote improved functional mobility. A trend reported by Brar et al. and clinical observation suggests that the beneficial effects of baclofen were noted when stretching exercises were added to the treatment.

Intravenous Methylprednisolone and Rehabilitation

Methylprednisolone administered intravenously (IVMP) is a common medical management in relapse of MS.[18] What had not been investigated until recently was the use of IVMP and multidisciplinary rehabilitation to promote recovery from relapse. Craig et al.[18] designed a study with the primary outcome measures of Guy's Neurological Disability Scale (GNDS) and Amended Motor Club Assessment (AMCA), and secondary measures of Barthel Index (BI), Human Activity Profile (HAP), and SF-36. Forty subjects, including 27 females, participated in the study. The authors reported statistically significant differences in GNDS (p=0.03), AMCA (p=0.03), HAPM (p<0.01), HAPA (p=0.02), and BI (p=0.02) at three months for those individuals receiving the multidisciplinary care. This study suggests that combining steroids with planned multidisciplinary care is superior to administering IVMP in a standard neurology or day ward setting.

Dalfampridine (Fampridine)

The dalfampridine extended-release tablet (AMPYRA™) is a new pharmaceutical agent that in laboratory studies has been found to improve impulse conduction in nerve fibers in which the insulating layer, or myelin, has been damaged.[19] Dalfampridine is a potassium channel blocker indicated as a treatment to improve walking in patients with MS. This was demonstrated by an increase in walking speed.[20] Historically, this compound has been referred to as fampridine. However, in order to eliminate potential name confusion with other marketed products, a new generic name, dalfampridine, has been established. Dalfampridine is also known by its chemical name, 4-aminopyridine (4-AP).

A recent study of dalfampridine by Goodman et al. in 2007[21] reported a prospectively analyzed increase in lower-extremity muscle strength in the dalfampridine group compared with placebo (unadjusted p-value 0.01). Improvement in walking speed, analyzed *post hoc*, was also seen in the dalfampridine group compared with placebo (unadjusted p-value 0.03). The recommendation from this study was that future studies should evaluate doses of up to 20mg twice daily, with lower-extremity strength and walking speed as potential outcome measures.

A follow-up study by Goodman and colleagues in 2008[22] evaluated walking speed over a 12-week stable-dose period for patients on a 10, 15, or 20mg twice-daily dose of dalfampridine. Trends for increased walking speed were consistent across dose groups compared with placebo, and an increase from baseline in lower-extremity strength during the 12-week stable-dose period was reported in the 10 and 15mg groups compared with placebo (p=0.018 and p=0.003, respectively). A *post hoc* analysis showed that subsets of patients in the dalfampridine groups had walking speeds that were consistently faster during the treatment period compared with the non-treatment period. These patients were defined as responders. There were significantly more responders in the dalfampridine groups compared with placebo (36.7 and 8.5%, respectively). Self-report on the 12-item MS Walking Scale (MSWS-12) showed significantly greater improvement in self-assessed ambulation in dalfampridine responders compared with non-responders.

In 2009, Goodman et al.[23] reported improvement in walking speed in dalfampridine-treated timed walk responders, which was maintained throughout the treatment period, of 25.2% (95% CI 21.5–28.8%) in the treated group and 4.7% (95% CI 1.0–8.4%) in the placebo group. Timed walk responders showed greater improvement in MSWS-12 scores (-6.84, 95% CI -9.65 to -4.02) than timed walk non-responders (0.05, 95% CI -1.48–1.57; p=0.0002).

Exercise and Brain-derived Neurotrophic Factor

One of the most exciting areas of investigation in the area of exercise and MS is the production of neurotrophins such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF).[24] These neurotrophins are thought to play an important role in neuronal repair and plasticity, and recent experimental evidence suggests neuroprotective effects of these proteins in MS.[24] In a study conducted by Gold et al. in 2003,[24] basal NGF levels were significantly elevated in MS in response to acute exercise. Thirty minutes of moderate exercise significantly induced BDNF production in people with MS and control subjects. The authors concluded that moderate exercise may be used to induce neutrophin production in humans.

In a study by White and Castellano,[25] 11 individuals with MS and 11 age-matched controls completed an eight-week exercise program consisting of a three-minute warm-up at a self-assessed comfortable speed followed by 30 minutes of cycle ergometry at 60% of VO_2 max, three times per week. In this particular study, elevated resting serum BDNF was found following four weeks of exercise training, with a return to baseline at week eight in the MS group only. Similar observations have been reported in healthy animal models. At the end of the eight-week training period, BDNF levels in the subjects with MS had returned to baseline values. Exercise immunomodulation appears to be mediated by a complex interaction of hormones, cytokines, and neural factors that may favorably influence immune variables in MS and may have neuroprotective effects.[25] Further investigation is needed in this area.

Meta-analyses and Cochrane Reviews

Five reviews, meta-analyses, and Cochrane reviews have been published since 2001 summarizing the research in exercise and MS. The earliest report, published by Baker and Tickle-Degnen in 2001,[26] was a meta-analysis of current best evidence for the use of occupational therapy for individuals with MS. Twenty-three articles were reviewed that examined the effectiveness of occupational-therapy-related treatments on individuals with MS. Meta-analysis suggested that occupational-therapy-related treatments were effective in treating the deficits associated with MS (r=0.52), such as muscle strength, range of motion, and mood, as well as addressing task and activity performance, such as dressing and bathing (r=0.57). After review of the study designs, it was stated that more rigorous research is necessary to fully understand treatment effectiveness.

A Cochrane review performed by Reitberg et al. in 2005[3] produced nine high-methodological-quality RCTs (260 participants) that met the inclusion criteria. Six trials focused on comparison of exercise versus no exercise, with the remaining three trials comparing two different exercise interventions. The best evidence was strongly in favor of exercise compared with no exercise in terms of muscle power function, exercise tolerance functions, and mobility-related activities.[3] Moderate evidence was found for improving mood, but no evidence was observed for the effect of exercise on fatigue.[3] The authors concluded that exercise can be beneficial for patients with MS who are not experiencing an exacerbation.

Dalgas et al. in 2008[27] conducted a review and concluded that evidence exists for recommending participation in endurance training at low to moderate intensity. Resistance training of moderate intensity was also reported to be well tolerated; however, the authors stated that the methodological quality of the existing evidence was not strong and the number of studies was limited.

In the same year, Motl and Gosney[28] published a meta-analysis on the effects of exercise training on quality of life. The cumulative evidence supported that exercise training is associated with a small improvement in quality of life among individuals with MS.

Most recently, in 2009 Asano et al.[29] identified 11 RCTs that were acceptable to their methodological investigation and concluded that there was insufficient research in this area, making it difficult to guide regular exercise prescription. Furthermore, the authors emphasized the methodological challenges in these RCTs and the need for high-quality research to establish evidence for regular exercise and physical activity prescription for persons with MS.

Health and Wellness

"People with multiple sclerosis have a lifelong need for physiotherapy and exercise interventions due to the progressive nature of the disease and their greater risk of the complications of inactivity."[30] A study has been initiated by Coote and colleagues in conjunction with the Multiple Sclerosis Society of Ireland to examine which form of physical activity might optimize physical and quality of life outcomes for people living with MS. The study will examine the benefits of physiotherapy, yoga, and exercise classes for their members. As stated in the introduction, physical inactivity in itself may contribute to a worsening of symptoms in this population. If we can identify exercise programs that optimize health and wellness, we can have a more positive impact on overall quality of life. As reported by Donze, "rehabilitation is one of the treatments of MS patients and should be viewed as an ongoing process to maintain and restore maximum function and quality of life."[31]

Conclusion

It is a well recognized fact that exercise is an important component in promoting health and wellness in the general population. For individuals living with MS, exercise and rehabilitative interventions play an important role in symptom management, enhancing cardiovascular function and promoting motor recovery. RCTs are needed to demonstrate specific neuro-rehabilitative techniques and exercise interventions that result in improved function and motor recovery. ■

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1. National MSS, *Multiple Sclerosis Information Sourcebook*, Information Resource Center and Library of the National Multiple Sclerosis Society, 2005.
2. Motl RW, et al., Worsening of symptoms is associated with lower physical activity levels in individuals with multiple sclerosis, *Mult Scler*, 2008;14(1):140–42.
3. Rietberg MB, et al., Exercise therapy for multiple sclerosis, *Cochrane Database Syst Rev*, 2005(1).
4. Gehlsen GM, et al., Effects of an aquatic fitness program on the muscular strength and endurance of patients with multiple sclerosis, *Phys Ther*, 1984;64(5):653–7.
5. Chen WY, et al., Force–time measurements of knee muscle functions of subjects with multiple sclerosis, *Phys Ther*, 1987;67(6):934–40.
6. Brar SP, et al., Evaluation of treatment protocols on minimal to moderate spasticity in multiple-sclerosis, *Arch Phys Med Rehabil*, 1991;72(3):186–9.
7. Petajan JH, et al., Impact of aerobic training on fitness and quality of life in multiple sclerosis, *Ann Neurol*, 1996;39(4): 432–41.
8. White LJ, et al., Resistance training improves strength and functional capacity in persons with multiple sclerosis, *Mult Scler*, 2004;10(6):668–74.
9. Gutierrez GM, et al. Resistance training improves gait kinematics in persons with multiple sclerosis, *Arch Phys Med Rehabil*, 2005;86(9):1824–9.
10. Bjarnadottir OH, et al., Multiple sclerosis and brief moderate exercise. A randomised study, *Mult Scler*, 2007;13(6):776–82.
11. van den Berg M, et al., Treadmill training for individuals with multiple sclerosis: a pilot randomised trial, *J Neurol Neurosurg Psychiatry*, 2006;77(4):531–3.
12. Benedetti MG, et al., Treadmill exercise in early mutiple sclerosis: a case series study, *Eur J Phys Rehabil Med*, 2009;45(1):53–9.
13. Crayton H, et al., A multimodal approach to managing symptoms of multiple sclerosis, *Neurology*, 2004;63(11): S12–S18.
14. Mathiowetz VG, et al., One-year follow-up to a randomized controlled trial of an energy conservation course for persons with multiple sclerosis, *Int J Rehabil Res*, 2007;30(4):305–13.
15. Gentry T, PDAs as cognitive aids for people with multiple sclerosis, *Am J Occup Ther*, 2008;62(1):18–27.
16. Bovend'Eerdt TJ, et al., The effects of stretching in spasticity: A systematic review, *Arch Phys Med Rehabil*, 2008;89(7):1395–1406.
17. Motl RW, et al., Effect of acute leg cycling on the soleus H-reflex and modified Ashworth scale scores in individuals with multiple sclerosis, *Neurosci Lett*, 2006;406(3):289–92.
18. Craig J, et al., A randomised controlled trial comparing rehabilitation against standard therapy in multiple sclerosis patients receiving intravenous steroid treatment, *J Neurol Neurosurg Psychiatry*, 2003;74(9):1225–30.
19. www.drugs.com/nda/fampridine_sr_090202.html (accessed November 29, 2009).
20. www.medscape.com/viewarticle/588839 (accessed November 29, 2009).
21. Goodman AD, et al., Fampridine-SR in multiple sclerosis: a randomized, double-blind, placebo-controlled, dose-ranging study, *Mult Scler*, 2007;13(3):357–68.
22. Goodman AD, et al., Dose comparison trial of sustained-release fampridine in multiple sclerosis, *Neurology*, 2008;71(15):1134–41.
23. Goodman AD, et al., Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial, *Lancet*, 2009;373(9665):732–8.
24. Gold SM, et al., Basal serum levels and reactivity of nerve growth factor and brain-derived neurotrophic factor to standardized acute exercise in multiple sclerosis and controls, *J Neuroimmunol*, 2003;138(1–2):99–105.
25. White LJ, Castellano V, Exercise and brain health – Implications for multiple sclerosis – Part II – Immune factors and stress hormones, *J Sports Med*, 2008;38(3):179–86.
26. Baker NA,Tickle-Degnen L, The effectiveness of physical, psychological, and functional interventions in treating clients with multiple sclerosis: A meta-analysis, *Am J Occup Ther*, 2001;55(3):324–31.
27. Dalgas U, et al., Multiple sclerosis and physical exercise: recommendations for the application of resistance-, endurance- and combined training, *Mult Scler,* 2008;14(1): 35–53.
28. Motl RW, Gosney JL, Effect of exercise training on quality of life in multiple sclerosis: a meta-analysis, *Mult Scler*, 2008;14(1):129–35.
29. Asano M, et al., What does a structured review of the effectiveness of exercise interventions for persons with multiple sclerosis tell us about the challenges of designing trials?, *Mult Scler*, 2009;15(4):412–21.
30. Coote S, et al., Getting the Balance Right: A randomised controlled trial of physiotherapy and Exercise Interventions for ambulatory people with multiple sclerosis, *BMC Neurol*, 2009;9.
31. Donze C, Neurorehabilitation in multiple sclerosis: an overview, *Rev Neurol (Paris)*, 2007;163(6–7):711–19.