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Exercise and Multiple Sclerosis

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Abstract

The pathophysiology of multiple sclerosis (MS) is characterised by fatigue, motor weakness, spasticity, poor balance, heat sensitivity and mental depression. Also, MS symptoms may lead to physical inactivity associated with the development of secondary diseases. Persons with MS are thus challenged by their disability when attempting to pursue an active lifestyle compatible with

health-related fitness. Although exercise prescription is gaining favour as a therapeutic strategy to minimise the loss of functional capacity in chronic diseases, it remains under-utilised as an intervention strategy in the MS population. However, a growing number of studies indicate that exercise in patients with mild-to-moderate MS provides similar fitness and psychological benefits as it does in healthy controls.

We reviewed numerous studies describing the responses of selected MS patients to acute and chronic exercise compared with healthy controls. All training studies reported positive outcomes that outweighed potential adverse effects of the exercise intervention. Based on our review, this article highlights the role of exercise prescription in the multidisciplinary approach to MS disease management for improving and maintaining functional capacity. Despite the often unpredictable clinical course of MS, exercise programmes designed to increase cardiorespiratory fitness, muscle strength and mobility provide benefits that enhance lifestyle activity and quality of life while reducing risk of secondary disorders. Recommendations for the evaluation of cardiorespiratory fitness, muscle performance and flexibility are presented as well as basic guidelines for individualised exercise testing and training in MS. Special considerations for exercise, including medical management concerns, programme modifications and supervision, in the MS population are discussed.

Multiple sclerosis (MS) is thought to be an autoimmune disorder that leads to the destruction of myelin, oligodendrocytes and axons.[1] Functional impairments in MS such as abnormal walking mechanics, poor balance, muscle weakness and fatigue typically result from axonal degeneration and conduction block. Although the exact aetiology of MS remains unknown, a combination of genetic, infectious, environmental and/or autoimmune factors likely contribute to disease onset. MS is the most common disabling neurological disease of young adults in the US.[2] The average person in the US has about a 1 in 750 chance of developing MS. The risk for a young person who has a parent with MS increases to 1 in 40.[2]

Disability in MS is related to reduced mobility, abnormal gait mechanics, poor balance and muscle weakness, as well as cognitive and autonomic dysfunction.[3] These impairments typically decrease functional capacity, contribute to fatigue, reduce daily activity and consequently increase the risk of secondary diseases such as coronary heart disease,[4] diabetes mellitus and obesity.[5] Decreased functional capacity is generally associated with greater MS disease severity. However, fitness testing can disclose compromised physical performance even in minimally impaired ambulatory MS patients.[6]

The incorporation of formal exercise and lifestyle activity early in the disease course may reduce the rate of decline in functional capacity observed in the MS population. Surprisingly, the effect of exercise therapy in the treatment of MS remains relatively unexplored[7,8] compared with, for example, research in cardiac rehabilitation; perhaps because until recently exercise was thought to magnify MS-related fatigue and other symptoms.[9] However, current studies suggest that individualised exercise in MS can promote many important therapeutic outcomes, such as improved cardiorespiratory[7,10-12] and muscle function[7,13-15] while decreasing depression[7,16] and fatigue,[3,12,13] toward promotion of health and quality of life. This review emphasises the adjunctive therapeutic role of exercise in the coordinated treatment plan for persons with MS.

1. Pathophysiology of Multiple Sclerosis (MS)

MS is a demyelinating inflammatory disease of the CNS with subsequent destruction of myelin, oligodendrocytes and axons.[1] It shows a distinct sexual bias with women having MS almost

2.5-times more often than men.[17] The disease process involves the activation and transport of inflammatory cells into the brain. The exact sequence of events that lead to myelin and axonal damage are yet to be defined, but increased activation of natural killer cells to attack myelin proteolipid protein characterises the pathogenesis of MS.[18] The clinical sequelae of demyelination provides the basis for diagnosis and treatment. Disease patterns in MS are progressively more disabling, including: relapsing remitting, primary progressive, secondary progressive and progressive relapsing, respectively.

Demyelination compromises nerve fibre function by slowing axonal conduction velocity. Axonal injury or death may also occur.[19] Altered conduction in demyelinated motor and sensory tracts within the CNS can disturb gait and balance, increase the risk of falls and reduce daily lifestyle activity. Balance and coordination are compromised when demyelination also affects the proprioceptive, visual and vestibular pathways. Vertigo, imbalance, incoordination, gait disturbances and spastic movements all contribute to mobility problems. Muscle weakness and fatigue, one of the most prevalent symptoms in MS, further reduce walking tolerance and contribute to the need for ambulatory assistance. Furthermore, atrophic changes associated with decreased voluntary physical activity further contribute to the decline in muscle strength, functional capacity and quality of life. Individuals with MS, therefore, face profound physical and psychological challenges as they negotiate the course of their disease.

The impact of MS on activities of daily living is influenced by the patient's functional capacity, disease progression and symptom management with pharmacological agents. As shown in table I, controlled exercise testing studies indicate that MS is associated with reduced levels of muscle strength,[20-23] speed,[24] endurance[25] and cardiorespiratory fitness[26-28] when compared with healthy subjects. Improving fitness in MS patients should help, therefore, to minimise their disability. Importantly, wide variation in physical capacity between patients necessitates testing for strength, flexibility and cardiorespiratory endurance in order to personalise the exercise prescription.

1.1 Fatigue

Fatigue unrelated to physical activity is a common symptom in MS that has been observed since the initial descriptions of this disease. Approximately 65% of individuals with MS report fatigue limitations[9,45-48] and as many as 40% describe it as the single most disabling symptom – a higher percentage than weakness, spasticity, balance or bowel/bladder problems.[49] MS fatigue is experienced in different forms, but is commonly expressed as a general (systemic) feeling of tiredness or lassitude[33,49] or as muscle fatigue without exercise.[22,41] Although systemic fatigue is highly variable between patients, it usually interferes significantly with activity at home or work. Cognitive fatigue, as indicated by reduced attention, memory [50,51] and information processing have also been reported.

The pathophysiology of fatigue in MS patients remains unexplained. Wide differences in MS-related fatigue between patients suggest multifactorial causes. Some investigations have focused on immune[52-57] and neuromuscular mechanisms.[22,39,40,58] Others have indicated that brain metabolism may also become altered in MS patients.[59-61] Systemic fatigue generally worsens throughout the day.[62] Environmental heat and humidity can dramatically increase both systemic fatigue and exercise-related fatigue, whereas cooling typically alleviates symptoms.[47,48] Pharmacological agents used to treat MS fatigue include fampridine, amantadine, the CNS stimulant pemoline, and the wake-promoting agent modafinil. Recently, levacecarnine supplementation (1g twice daily) was found in a randomised, double-blind, crossover study, more effective and better tolerated than amantadine (100mg twice daily) for the treatment of MS-related fatigue.[63] Regular physical activity may also alleviate fatigue while enhancing functional reserve capacity.[7,12,13]

1.2 Muscle Weakness

Reduced muscle strength is a major impairment that limits activities of daily living. Studies have shown lower isometric force, isokinetic force, isotonic force and total work of the quadriceps in MS patients[20,32,33,35,37,42] (table I). Chen et al.,[42] Ng et al.[36] and Nielsen and Norgaard[31] found that MS

Table I. Functional measures in patients with multiple sclerosis (MS) and controls (C)

Study (year)	Variables	Sample size	Disability (EDSS)	Protocol	Results
Mevellec et al.[29] (2003)	Muscle strength and gait mechanics	27 MS, 10 C	<6	Gait speed evaluated with locometer that records displacement of each foot. Peak torque of quadriceps and hamstrings measured with isokinetic dynamometer	No significant differences in spontaneous and maximal gait speed or peak torque between groups. Gait speed and hamstring torque were correlated in MS with proprioceptive loss
Gold et al.[30] (2003)	Serum NGF and BDNF levels	48 MS, 20 C	<5	30 min cycle ergometry at 60% $\dot{V}O_{2max}$	Basal NGF was higher in MS while basal BDNF was not different. NGF and BDNF increased after exercise in both MS and C
Nielsen and Norgaard[31] (2002)	MEP after non-fatiguing exercise	15 MS, 10 C	Ambulatory	Isometric contractions of biceps brachii muscle at 25%, 50% and 100% MVC for 6 sec	Significant post-exercise increase in MEP amplitude in MS compared with C being most pronounced after a contraction for 6 sec. The post-exercise increase in MEP lasted for >30 sec in MS compared with C
de Ruiter et al.[32] (2001)	Muscle force, velocity and fatigue	12 MS, 8 C	2–6	Electrical stimulation of the adductor pollicis	No significant differences in maximal stimulated isometric force, rate of force development or fatigue
Lambert et al.[33] (2001)	Muscle strength and muscle fatigue in the knee flexors and extensors	30 MS, 30 C	<5	Five isokinetic leg extensions and flexions on a Cybex isokinetic dynamometer for strength testing followed by 2 min rest. Three bouts of 30 concentric flexions and extensions separated by 1 min rest for fatigue test	Peak torque adjusted for age, body mass and fat-free mass was significantly greater for C than for MS for three of four lower body muscle groups tested. Total work was significantly greater for C than MS for the flexors (group effect) and approached significance for the extensors
White et al.[34] (2000)	Fatigue and 7.6m (25ft) walk time before and after pre-cooling	6 MS, 0 C	Thermosensitive/ ambulatory	Subjects pre-cooled by immersion of lower body in 16–17°C water for 30 min. Fatigue assessed after 30 min exercise at 60% $\dot{V}O_2$ on an arm/leg ergometer	No difference in $\dot{V}O_2$ after pre-cooling. Rectal temperature, HR and RPE were lower during exercise after pre-cooling. Pre-cooling improved fatigue scores. 7.6m walk performance and fatigue scores showed significantly greater deterioration in the noncooled condition
Petajan and White[23] (2000)	MEP and central conduction time after handgrip exercise	32 MS, 10 C	MS with weakness (16) and normal motor function (16)	3 min sustained maximal handgrip exercise. PCr measured post-exercise	MS had lower MVC than C. MEPs after exercise were higher in C and normal motor function group than in MS with weakness. Exercise prolonged central motor conduction in MS but not in C

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Table I. Contd

Study (year)	Variables	Sample size	Disability (EDSS)	Protocol	Results
de Haan et al.[35] (2000)	Quadriceps strength	17 MS, 16 C	2–6	Quadriceps strength tested during voluntary and electrically stimulated contractions	The estimated maximal isometric force-generating capacity of MS was 11.2% ($p < 0.05$) lower than C. MS were able to voluntarily exert 75 ± 22% (n = 12) of their maximal capacity vs 94 ± 6% (n = 7) for C. During a series of repeated contractions, greater decrements occurred in isometric force and in maximal rate of force rise in MS by 31.3 ± 10.3% and 50.1 ± 10.0%, respectively, (n = 13) than C (23.8 ± 6.6% and 39.0 ± 8.1%, n = 15)
Ng et al.[36] (2000)	Muscle endurance, muscle pH and Pi concentration, HR and mean arterial pressure	9 MS, 11 C (subset 6 MS, 10 C)	2–6	Isometric contraction of the dorsiflexor at 30% MVC until failure while monitoring intramuscular pH and Pi using P-MRS	Endurance times at 30% MVC and change in HR were similar in MS and C. The decrease in pH and increase in Pi were less throughout exercise in MS compared with C, as was the change in MAP response
Schwid et al.[37] (1999)	Reliability of strength and fatigue measurements	20 MS, 20 C	1.5–6.5	MVC of seven muscle groups using fixed myometry. Fatigue was assessed during static and repetitive maximal contractions as well as walking 8m as fast as possible and walking the maximum distance subjects could walk (as far as 500m)	Test-retest reliability was lower for exercise protocols that involved repetitive contractions or ambulation. Compared with healthy C, MS were weak in lower extremity muscles, but upper extremity strength was relatively preserved. Fatigue was greater in MS. There were no significant associations between strength and fatigue in any of the muscles tested
Iriarte and de Castro[20] (1998)	Correlation between fatigue symptoms and handgrip endurance	50 MS, 50 C	2.2 ± 1.9	Isometric and isotonic handgrip exercise to test for MVC and endurance	Lower isometric and isotonic strength in MS, but recovery was similar to C. Symptoms of fatigue correlated inversely with endurance in MS
Chiara et al.[38] (1998)	$\dot{V}O_2$, RPE and spasticity	14 MS, 0 C	<5	10 min walk before and after cold water bath (24°C)	Spasticity was higher immediately after cold bath while $\dot{V}O_2$ and RPE were not significantly different in MS vs C

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Table I. Contd

Study (year)	Variables	Sample size	Disability (EDSS)	Protocol	Results
Sheean et al.[24] (1997)	Isolated muscle fatigue	21 MS, 19 C	5.4 ± 1.9	45 sec MVC of the adductor pollicis	The strength of C declined by ≈20% during the contraction. MS had normal baseline strength, but declined by ≈45% during the contraction. C showed no significant change in central activation throughout the exercise, but MS showed a significant decline in central activation ($p < 0.001$). Decline in speed after fatigue was similar to C
Latash et al.[21] (1996)	Myogenic and central neurogenic fatigue	11 MS, 11 C	3–5	Quadriceps electrically stimulated during sustained contractions at 0–100% of MVC on a Kin-Com dynamometer	Decreased torque at 75–100% MVC in MS. E-stim was able to restore torque in MS
Pepin et al.[26] (1996)	BP and HR responses to isometric exercise	104 MS, 25 C	No EDSS scores documented	Isometric handgrip exercise at 30% of MVC to fatigue	Systolic, diastolic and MAP increased linearly in both groups, but were significantly lower in MS at 20%, 40%, 60%, 80% and 100% of exercise duration. HRs in C were significantly higher than MS ($p < 0.05$) at 20% of exercise duration. No significant difference in HR response at 40%, 60%, 80% and 100%
Sharma et al.[22] (1995)	Muscle PCr and pH, tetanic force of the electrically stimulated tibialis anterior	28 MS, 14 C	2–8	9 min of intermittent e-stim	MS had lower tetanic force and greater decline of tetanic force than C. PCr declined more rapidly in MS. PCr recovery was complete in both groups after 15 min
Kent-Braun et al.[39] (1994)	Muscle Pi, PCr and pH after exercise	13 MS, 8 C	4.2 ± 0.8	Intermittent tetanic contractions of the dorsiflexor muscles by e-stim of the peroneal nerve	No significant differences in pH or PCr compared with C during the exercise. Slowed PCr recovery after exercise in MS compared with C
Kent-Braun et al.[40] (1994)	Muscle metabolism during exercise and recovery	6 MS, 8 C	Mild MS	Intermittent, progressive, isometric contractions of the ankle dorsiflexors, measuring MVC, Pi, PCr, and pH using P-MRS	MVC similar between MS and C at the end of the exercise. Restoration of Pi/PCr ratio slower in MS compared with C ($p < 0.01$). At the end of exercise, MS pH remained unchanged while C pH had decreased ($p < 0.01$)

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Table I. Contd

Study (year)	Variables	Sample size	Disability (EDSS)	Protocol	Results
Foglio et al.[25] (1994)	Arm exercise capacity, respiratory muscle function and arterial blood gases	24 MS, 0 C	5.3 ± 2	Incremental exercise test on an arm ergometer	16 of the 24 patients were able to complete the exercise test (group 1), the other eight were not (group 2). Inspiratory muscle endurance time was significantly lower in group 2 compared with group 1. Arterial blood gases were normal in all patients
Tantucci et al.[28] (1994)	Ventilatory muscle strength and function, and cardiorespiratory response to incremental exercise	11 MS, 10 C	6.7 ± 1.2	Respiratory muscle strength was assessed by measuring maximal inspiratory and expiratory mouth pressures, respectively	MS had lower inspiratory and expiratory pressure. A significant inverse correlation was found between both inspiratory and expiratory pressure at functional residual capacity and the severity score of the disease. The inspiratory drive at rest is increased and the drive response to CO_2 appears normal, while the ventilatory response to CO_2 is significantly impaired in MS
Rice et al.[41] (1992)	Muscle tension development	4 MS, 0 C	3.5–6	Electrical stimulation of the quadriceps using an isometric dynomometer at 95°	MS subjects rarely achieved >60% activation. Firing rates in MS rarely exceeded 17Hz compared with 24Hz in C
Chen et al.[42] (1987)	Muscle tension development, maintenance and inhibition time	15 MS, 17 C	Ambulatory	Quadriceps and hamstrings were tested isometrically at 45° and isokinetically at 30 and 90°/sec	MS demonstrated a significant ($p < 0.001$) slowing of the time-rate of muscle tension development and a significant ($p < 0.005$) decrease in muscle tension-maintaining capacity when compared with C
Senaratne et al.[27] (1984)	Cardiovascular and autonomic dysfunction	21 MS, 20 C	No EDSS scores documented	Variation in HR during deep breathing, variations in HR and systolic BP during a standardised Valsalva manoeuvre, changes in HR and systolic BP during arm ergometry starting at 30W with increments of 20W every 3 min	Maximum variation in HR from inspiration to expiration was >16 beats/min (range 17–43) in controls. Five MS had a maximum variation in HR of <13 beats/min. The Valsalva ratio in C ranged from 1.33–3.24. Four MS had Valsalva ratios of <1.30. HR response to exercise was attenuated significantly in four MS ($p < 0.001$). BP responses to exercise were attenuated significantly in seven MS ($p < 0.001$)

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Table I. Contd

Study (year)	Variables	Sample size	Disability (EDSS)	Protocol	Results
Armstrong et al.[43] (1983)	Muscle strength	10 MS, 20 C	<5	Knee extensor and knee flexor contraction at selected angular velocities ranging from 0–275°/sec	MS extensor and flexor peak torques were significantly lower than C ($p < 0.005$ to $p < 0.001$) at all angular velocities. Mean extensor : flexor ratios for C and for MS were not significantly different at 70, 190 and 230°/sec
Cartlidge[44] (1972)	Sweat response and autonomic function	50 MS, 0 C	4–6	BP was measured in each arm after being supine for 15 min, immediately upon standing, and 1 min after walking 18m. Sweat response was measured by hot water submersion for 30 min	30 of the subjects had a normal sweat response. 20 were found to have impaired sweat response – three with no sweating below the nipples, four with no sweating below the waist and 13 with no sweating on the legs. BP measurements were normal. No orthostatic hypotension reported

BDNF = brain-derived neurotrophic factor; **BP** = blood pressure; **EDSS** = Expanded Disability Status Scale; **e-stim** = electrical stimulation; **HR** = heart rate; **MAP** = mean arterial pressure; **MEP** = motor-evoked potential; **MVC** = maximum voluntary contraction; **NGF** = nerve growth factor; **PCr** = phosphocreatine; **Pi** = inorganic phosphate; **P-MRS** = phosphorus magnetic resonance spectroscopy; **RPE** = rate of perceived exertion; $\dot{V}O_2$ = oxygen uptake; $\dot{V}O_{2max}$ = maximal oxygen uptake.

patients also had slower muscle tension development in isometric and isokinetic tests of the quadriceps and hamstrings. Mechanisms that contribute to reduced strength include decreased motor unit firing rates,[41] inadequate motor unit recruitment[41] and increased central motor conduction time.[64] Peripheral changes thought to contribute to muscle weakness include atrophy, lower oxidative capacity and a greater tendency for energy production via anaerobic metabolism.[39,40,58] Although MS patients may have compromised muscle performance that is disease related, decreased physical activity likely contributes to the observed atrophic changes.

1.3 Depression

Over 50% of MS patients experience depression.[65] One study found that the risk of suicide was 7.5-times higher among persons with MS than the general population.[66] Depression may develop from the initial MS diagnosis and the realisation that the disease may progress to permanent disability. The disease process and neuroendocrine changes possibly influence brain centres responsible for emotion and contribute to emotional lability. In addition, depression can be an adverse effect of some medications used to treat MS. The antidepressive value of regular aerobic exercise has been demonstrated in mild to moderate clinical depression.[16,67-69]

1.4 Spastic Paresis

Spastic paresis[70] is an upper motor neuron impairment that involves exaggerated tendon reflexes (hyperreflexia), resistance to passive stretch (hypertonia) and muscle weakness. Spasticity is a velocity-dependent increased resistance to muscle lengthening due to activation of tonic stretch reflexes.[71] Paresis refers to weakness, loss of dexterity and fatigability. Elevated temperature, humidity or infections may aggravate spasticity in MS. In contrast, whole-body cooling has also been shown to increase spasticity.[38] Therefore, extremes in temperature should be avoided to minimise spasticity in MS patients.

1.5 Poor Balance/Fall Risk

Maintaining dynamic balance relies on intact visual, somatosensory and vestibular input[72] combined with coordinated righting reflexes. The increased risk of falls in MS is complicated by poor judgement and compromised muscle strength and motor control.[73] Risk of fracture from falls in MS patients is 2- to 3.4-times higher than for a healthy control.[74] Cognitive deficits may also occur early in the MS disease course[75] and may impact information processing, attention, decision making, error correction and execution of function.[76] Changes in mental status may lead to poor judgment and slowed response time that contribute to fall risk.[77] Unfortunately, heightened awareness of injury risk and the fear of falling can further reduce mobility and quality of life.

1.6 Respiratory Diseases

Ventilatory muscle weakness in MS contributes to the inability to produce an effective cough and thereby predisposes patients to respiratory diseases.[78,79] Expiratory muscle weakness can occur relatively early in the disease[54,80,81] and may become more pronounced as disability increases. Compromised inspiratory muscle strength has also been reported.[25] Lobar pneumonia and aspiration pneumonia are the most common disease-related causes of mortality in MS patients.[78,79] Consequently, specific exercises for training ventilatory muscles to reduce decrements in pulmonary function are likely to have important therapeutic benefits in this population. In addition, aerobic exercise training can also improve ventilatory muscle performance in patients with MS.[12]

1.7 Elimination Dysfunction

The most common bladder control problems in MS are urgency, frequency and incontinence. Elimination dysfunction is estimated to affect approximately 80% of MS patients during the course of their disease.[82] Manifestations of bladder dysfunction include: (i) reduced storage, in which the bladder is hyperactive and holds only a small amount of urine before urgency; and (ii) reduced emptying, in which the bladder retains an excessive amount of urine. Retention of stagnant urine predisposes MS patients to urinary tract infection as well as bladder and renal calculi. Bowel dysfunction is reported in approximately 60% of patients.[83] Constipation, the most common bowel problem, results from a range of causes including pelvic floor spasticity, decreased gastro-colic reflex, inadequate hydration, medications, immobility, poor general physical fitness and weak abdominal muscles.[84] Because incontinence can cause exercise anxiety in the MS patient, scheduling for time of day and breaks during the exercise programme are important considerations.

1.8 Secondary Diseases in MS

MS patients often have low participation in physical activity behaviours.[85] Since physical inactivity is a major coronary heart disease risk factor,[86] persons with MS may be at additional age-related risk for heart disease. Slawta et al.[4] found that light and moderate physical activity in leisure time was associated with less abdominal fat accumulation, lower serum triglyceride and lower glucose levels in female MS patients, suggesting that leisure-time activity may reduce coronary risk and contribute to clinically relevant health benefits in women with MS. A 2-month exercise programme was found to decrease CHD risk indicators in some MS patients.[87]

The increasing prevalence of obesity in the general population includes persons with MS.[5] Reduced mobility and fatigue in MS contribute to reduced daily energy expenditure and the potential for weight gain. The role of exercise in modifying weight gain has important clinical implications. For example, reducing excess weight through exercise may reduce fatigability during activity, risk of falls and morbidity, as well as enhance self-esteem.[86]

2. Medical Management of MS

2.1 Disease-Modifying Agents

The management of MS has been substantially advanced by the availability of disease-modifying agents such as those shown in table II. A number of positive outcomes in relapsing-remitting MS have been demonstrated using these agents, including reduction in the frequency and severity of relapses, reduction of brain lesion development, as evidenced

Table II. Common multiple sclerosis (MS) disease-modifying agents

Drug name	Trade name[a]	Action	Treatment and dosage
IFNβ-1a	Avonex®	Immunomodulator	For the treatment of relapsing forms of MS and single clinical episodes if MRI features consistent with MS are also present. Weekly IM injections of 30μg
IFNβ-1a	Rebif®	Immunomodulator	For treatment of relapsing forms of MS. SC injections 44μg, 3 d/wk
IFNβ-1b	Betaseron®	Immunomodulator	For the treatment of relapsing forms of MS, including secondary-progressive MS. SC injections every other day
Glatiramer acetate	Copaxone®	Immunomodulator	For the treatment of relapsing-remitting forms of MS. SC injections 20mg (20 000μg) daily
Mitoxantrone	Novantrone®	Immunosuppresant	For treatment of rapidly worsening relapsing-remitting MS and for lifetime progressive-relapsing or secondary-progressive MS. IV infusion 4 times/year (limit 8–12 doses)

a The use of trade names is for product identification purposes only and does not imply endorsement.

IFN = interferon; **IM** = intramuscular; **IV** = intravenous; **MRI** = magnetic resonance imaging; **SC** = subcutaneous.

by magnetic resonance imaging and possible reduction of future disability. Immune modulating therapy is primarily indicated for patients with relapsing-remitting disease or some cases in progressive relapsing disease. However, only 50% of patients with clinically definite MS are thought to receive immunomodulating therapy that might reduce the rate of disease progression.[88]

In addition to the primary drugs to reduce disease progression, other agents may be taken for the comorbidities of MS, including depression, systemic fatigue, bowel/bladder dysfunction and spasticity, as well as medications for secondary health complications such as cardiovascular and pulmonary disorders and diabetes. Consequently, MS patients may take a wide variety of medications that should be considered when designing the exercise programme.

2.2 Treatments for Elimination Dysfunction

Suggested treatments for urinary dysfunction include avoidance of dietary bladder irritants such as alcohol, aspartame and caffeine. Specific medications for bladder control include tolterodine and oxybutynin. Anticholinergic drugs are sometimes prescribed to reduce bladder hyperactivity. Bowel dysfunction includes constipation and/or involuntary bowel movements. To reduce constipation, daily intake of adequate dietary fibre and sufficient hydration of 1–2 L/day of fluid are recommended. Experience suggests that exercise may be an important stimulant for promoting regular evacuation. Kegel exercises for the pelvic floor muscles may also help in bladder and bowel control.[89]

2.3 Antispasmotic Drugs

Management of spastic paresis includes rehabilitation techniques to train and develop residual motor function and to prevent secondary complications such as contractures.[90] Antispasmotic drugs may be prescribed in severe cases and their mechanism of action involves increased presynaptic inhibition of group I afferents and reduction of the myotactic reflex (baclofen, tizanidine, clonazepam, diazepam), inhibition of excitatory interneurons in the spinal reflex pathway (tizanidine, glycine) or reduced muscle contractility (dantrolene).[90]

3. Exercise Testing and Training in MS

Although current research indicates that MS patients can gain a wide variety of therapeutic and functional benefits from regular activity, the influence of exercise on the progression of MS symptoms remains unclear and additional studies are warranted. Importantly, prescribed exercise does not appear to increase the rate or severity of MS exacerbations in patients.[7] The primary benefits of regular exercise in MS include increased cardiorespiratory fitness,[7,10-12] muscle strength and endurance,[7,13,91] reduced systemic fatigue,[7,12,13] improved mood[12,14,15,92] and enhanced ability to perform tasks of daily living with increased vigour. Exercise is considered helpful in managing common MS symptoms and promoting wellness. For example, Petajan et al.[7] found that regular aerobic exercise was associated with better bladder and bowel function, less fatigue and depression, a more positive

attitude and increased participation in social activities. Regular exercise is also desirable for reducing the risk of comorbidities such as obesity, heart disease, diabetes and osteoporosis. In contrast, muscle weakness, decreased bone density with an increased risk of fracture and inefficient breathing patterns are consequences of physical inactivity.[25]

This review focuses on the effects of exercise, mainly in ambulatory MS patients. Studies cited used the Expanded Disability Status Scale (EDSS) to classify patient clinical status.[93] The EDSS is the most widely applied classification of neurological impairment in MS, although it has been criticised for the absence of adequate cognitive and visual components, emphasis on ambulation status, relatively reduced sensitivity in the middle and upper ranges of scores.[94] The EDSS quantifies disability in eight functional systems and allows physicians or trained healthcare professionals to assign a functional system score in each of the following areas: pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral and other.[93] The functional systems are rated on a scale of 0 (normal function) to 5–6 (unable to perform normal functions). EDSS scores ranging from 1–4.5 indicate patients who are fully ambulatory while scores of ≥5 indicate ambulation impairment. A simplified version of the EDSS is shown in table III. There is also a self-administered EDSS that patients may use to evaluate their own level of disability.[95]

4. Training Responses

Table IV summarises studies that have measured adaptations to aerobic exercise and strength training in the MS population. The training intervention period and prescribed intensity and duration of exercise vary between studies. However, all studies indicate that selected and supervised patients with MS are capable of making favourable improvements in fitness with a minimal risk for serious adverse effects of prescribed training.

Table III. Abbreviated Expanded Disability Status Scale[93]

Score	Function
1.0	Normal neurological examination
2.0	Minimal disability
3.0	Moderate disability
4.0	Ambulatory without aid 12h
5.0	Disability impairs activity (walk without aid 300m)
6.0	Intermittent or unilateral constant assistance
7.0	Unable to walk 5m without aid
8.0	Essentially restricted to bed
9.0	Helpless bed patient
10	Death due to multiple sclerosis

4.1 Cardiopulmonary Fitness

Aerobic exercise training in MS is associated with increased maximal or peak oxygen uptake ($\dot{V}O_{2peak}$)[7,10-12] and functional capacity,[7,11,12] increased muscle strength and endurance,[12,91,92] improved lung function[12] and delayed fatigue.[12,92]

4.2 Muscle Strength and Endurance

Surprisingly few studies have reported the effects of resistance training on muscle strength and function in MS. However, studies by Kraft et al.[14,15] indicate that progressive resistance training improves muscle strength in MS patients[15] and the ability to perform common daily activities while also improving psychosocial wellbeing.[14] White et al.[96] reported that 8 weeks of twice weekly progressive lower limb resistance training improved leg strength, stepping ability and reduced fatigue while also favourably altering gait.[98] DeBolt and McCubbin[91] found that 8 weeks of home-based lower body resistance training with elastic bands improved leg extensor power but not measures of balance or mobility.

4.3 Bone Health

Shabas and Weinreb[74] surveyed 220 women with MS and found that 82% had a history of corticosteroid use and 53% had impaired mobility with increased risk of premature osteoporosis. However, despite having a risk of fracture 2- to 3.4-times above healthy controls, basic preventive measures were not being followed in this population.[74]

The use of therapeutic corticosteroids by MS patients has been shown to contribute to reduced bone density, through either a decreased rate of mineralisation and/or increased bone resorption rate.[99,100] In contrast, other studies suggest that corticosteroid use may not impact bone mineral density.[99,101] For example, Schwid et al.[100] speculated that corticosteroid use enhanced the sustaina-

Table IV. Exercise training studies in persons with multiple sclerosis

Study (year)	Variables	Sample size	Disability rating (EDSS)	Training protocol	Results
White et al.[96] (2004)	Leg strength, stepping, fatigue	8 MS	1–5	2mo twice weekly, one set of 8–15 reps	Leg strength and 3 min stepping increased Self-reported fatigue decreased
Oken et al.[97] (2004)	Cognitive measures, fatigue, mood	69 randomised to three groups: group 1 yoga; group 2 cycle; group 3 C. 57 completed the study	≤6	6mo weekly exercise class plus home exercise	Attention and alertness did not change with yoga or cycle exercise. Fatigue improved with yoga and cycle exercise; mood remained unchanged with yoga and cycle exercise
DeBolt and McCubbin[91] (2004)	Balance, mobility, leg power	19 MS 18 MSC	1.0–6.5	Home-based resistance exercise 5–10 min warm-up; 25–30 min strengthening exercise 5–10 min whole body stretching 3 ×/wk, 8wk	Balance: no significant differences between groups for any of the balance measures AP sway: −10.3% in MS and +6.4% in MSC; group by time interaction was not significant ML sway: −4% and MSC +9.4% Sway velocity: +2.5% and +25.1% in MSC Mobility: time decreased by −12.7% in MS, whereas MSC showed little improvement (+1.0%) Leg extensor power: +37.4% and MSC +6.7%
Mostert and Kesselring[12] (2002)	Lung function, cardiorespiratory activity level, fatigue, exacerbation symptoms, QOL	13 MS 13 MSC	MS: 2.5–6.5 MSC: 1.0–6.5	Cycling ergometer 30 min, 5 ×/wk, 4wk	Lung function: FVC +13%, FEV_1 +7%, PEFR +8%; MSC: PEFR +13% Work rate: +11% Activity level: sport-related +17% MSC: work-related +8% Fatigue: −14%; MSC +4% SF-36: vitality +46%; Social functioning +36; healthy active subjects social functioning +13% Maximum work rate: +11% Aerobic threshold: +12% MSC: −2% Work rate at aerobic threshold: 30%; MSC: +7%

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Table IV. Contd

Study (year)	Variables	Sample size	Disability rating (EDSS)	Training protocol	Results
					Oxygen pulse: +10%; MSC: +2% Gas exchange at zero-load pedalling: ($\dot{V}O_2$, HR and ventilation): no change HR: no change HR at given work rate: both MS groups decreased Ventilation at given work rate: both MS groups decreased up to 10% $\dot{V}O_{2max}$: +13% Symptom exacerbations: 10% of 63 graded exercise tests caused increased spasticity, araesthesia and vertigo 6% of 180 training sessions caused temporary symptom impairment
Husted et al.[92] (1999)	Walking speed (distance = 7.6m [25ft]), hamstring flexibility, QOL	19 MS	Not identified	T'ai Chi instruction 1h, 2 ×/wk, 8wk	Walking speed: +21% Hamstring flexibility: +28% SF-36 MS subjects (n = 19): physical functioning −9.59%; role physical 0%; bodily pain −6.9%; general health −10.63%; vitality +15.27%; social functioning +13.36%; role-emotional +2.08%; mental health +4.62%
Rodgers et al.[11] (1999)	Cardiorespiratory fitness ($\dot{V}O_{2max}$), ROM, gait mechanics	18 MS	1.0–6.5	Arm and leg ergometer or recumbent arm and leg bicycle 30 min, 65–70% HR_{max}, 3 ×/wk, 24wk	EDSS: no change $\dot{V}O_{2max}$: +15% Mean velocity: decreased from 0.79 to 0.72 m/sec Cadence: decreased from 0.8 to 0.7 steps/sec Maximum dorsiflexion angle: decreased Maximum plantarflexion angle: increased Total knee ROM in flexion and extension: decreased Maximum hip extension angle: decreased Total hip flexion/extension ROM: decreased

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Table IV. Contd

Study (year)	Variables	Sample size	Disability rating (EDSS)	Training protocol	Results
					Hip adduction: increased Hip abduction: decreased
					Ground reaction forces: −19%
					Passive ROM: hip abduction, adduction, external rotation and flexion when knee is extended increased Hip flexor: tightness increased
					Correlations: EDSS and velocity (r = −0.613), cadence (r = −0.572) and ground reaction forces (r = 0.613)
					Little effect of gait abnormalities and improved aerobic fitness
Ponichtera-Mulcare et al.[10] (1997)	Cardiorespiratory fitness ($\dot{V}O_{2max}$)	11 MS ambulatory, 8 MS semi-ambulatory, 4 MSC	1.0–4.5 5.0–6.5 1.0–6.5	Arm and leg ergometer or recumbent arm and leg bicycle 30 min, 55–60% $\dot{V}O_{2max}$, 3 ×/wk, 24wk	$\dot{V}O_{2max}$: subjects (ambulatory) +19% Subjects (semi-ambulatory) +7%, MSC −12% Correlations: EDSS and $\dot{V}O_{2max}$ pre-training showed a fair, negative relationship (r = −0.37), which improved slightly (r = −0.46) after training
Kraft et al.[14] (1996)	Mobility variables: WALK, CLIMB, CHAIR Self-reported disability: SIP	4 mild MS, 4 severe MS	Mild MS: 3.0 Severe MS: 6.0	PRE 3 ×/wk, 12wk	WALK: mild MS subjects increased by +11%, severe MS subjects increased by +2% CLIMB: mild MS subjects increased by +21%, severe MS subjects increased by +26%
					CHAIR: mild MS subjects increased by +17%, severe MS subjects increased by +14%
					SIP: mild MS changed: $t(3) = +3.43\%$, $p \leq 0.05$; severe MS changed: $t(3) = +3.17\%$, $p \leq 0.05$
					Psychosocial dimension component: mild MS changed: $t(3) = +2.71\%$, $p \leq 0.05$; severe MS changed: $t(3) = +2.74\%$, $p \leq 0.05$

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Table IV. Contd

Study (year)	Variables	Sample size	Disability rating (EDSS)	Training protocol	Results
					Physical dimension component: mild MS changed $t(3) = +2.80\%$, $p \leq 0.05$; severe MS changed: $t(3) = +34.00\%$, $p \leq 0.05$
Kraft et al.[15] (1996)	Muscle strength of: quadriceps, hamstrings, biceps, triceps	4 mild MS, 4 severe MS	Mild MS: 3.0 Severe MS: 6.0	PRE 3 ×/wk, 12wk	Mild MS subjects: quadriceps strength changed $t(3) = +3.78\%$; hamstrings strength $t(3) = +3.14\%$ biceps strength $t(3) = +2.50\%$; triceps strength $t(3) = +5.00\%$ Severe MS subjects: hamstrings strength $t(3) = +5.14\%$; biceps strength $t(3) = +4.00\%$; triceps strength $t(3) = +3.00\%$
Petajan et al.[7] (1996)	Fitness, clinical status, QOL	21 MS 25 MSC	2.6–6.0	Arm and leg ergometer 40 min, 60% $\dot{V}O_{2max}$, 3 ×/wk, 15wk	Functional systems: EDSS improved bowel, bladder scores Exacerbation rates: no significant difference $\dot{V}O_{2max}$: MS +22%; MSC +1% Physical work capacity: +44%; MSC +12% Functional aerobic impairment: subjects decreased from 21% to 5% Isometric strength: combined upper extremities +17%; combined lower extremities +11% Skinfold thickness: MS −6mm; MSC +2mm Blood lipids: triglycerides subjects −17% VLDL: decreased; TC, HDL, and LDL not changed POMS: depression decreased; anger decreased at wk 5 and 10 Fatigue: decreased at wk 10 SIP: total SIP improved at wk 10;

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Table IV. Contd

Study (year)	Variables	Sample size	Disability rating (EDSS)	Training protocol	Results
					Improved physical scores (ambulation, mobility at wk 10, body care and movement at wk 10); improved psychosocial scores (in only social interaction and emotional behaviour at wk 10); improved home management scores at wk 10; improved recreation and past times scores at wk 15 scores FSS: no change in either group Correlations: subjects: $\dot{V}O_{2max}$ and tension (r = −0.50), vigour (r = 0.39), fatigue (r = −0.68), POMS confusion (r = −0.40), SIP physical (r = −0.47), SIP psychosocial (r = −0.37), and FSS (r = −0.77) C: $\dot{V}O_{2max}$ and vigour, total SIP and SIP psychosocial
Gehlsen et al.[13] (1984)	Muscle strength and endurance of arms and legs	10 MS	Not identified	Freestyle swim and water calisthenics in 25–27.5°C water 1h, 60–75% HR_{max}, 3 ×/wk, 10wk	Dynamic peak torque: knee flexors not changed; knee extensors increased at 5wk Isometric peak torque: legs did not change Force: arms increased 46.7% to 85.0% Power: arms increased Total work: arms +39% at 5wk, 82% at 10wk; knee extensors +192% at 5wk, +330% at 10wk Fatigue: legs decreased −14%

AP = anteroposterior; **C** = subjects who do not have multiple sclerosis and do not exercise; **CHAIR** = up-and-go agility test; **CLIMB** = self-selected stair climbing; **EDSS** = Expanded Disability Severity Scale; **FEV_1** = forced expiratory volume in 1 second; **FSS** = Fatigue Severity Scale; **FVC** = forced vital capacity; **HDL** = high-density lipoprotein; **HR** = heart rate; **HR_{max}** = maximal heart rate; **LDL** = low-density lipoprotein; **ML** = mediolateral; **MS** = subjects with multiple sclerosis who exercise; **MSC** = subjects with multiple sclerosis who do not exercise; **PEFR** = peak expiratory flow rate; **POMS** = Profile of Mood States; **PRE** = progressive resistive exercise; **QOL** = quality of life; **reps** = repetitions; **ROM** = range of motion; **SF-36** = Short-Form 36; **SIP** = Sickness Impact Profile; **TC** = total cholesterol; **VLDL** = very low-density lipoprotein; **WALK** = self-selected ambulation velocity; **$\dot{V}O_2$** = oxygen uptake; **$\dot{V}O_{2max}$** = maximal oxygen uptake.

ble amount of weight-bearing activity, energy level and assisted in modifying bone loss through improved physical activity in MS patients. Further investigations are necessary to clarify the impact of therapeutic corticosteroid use on bone mineral density in MS patients during exercise training.

Osteoporosis is related to inactivity and is, therefore, a co-morbidity of MS. The disease process and motor limitations in MS likely lead to sarcopenia, which contributes to osteopenia. The decrease of bone density associated with inactivity further contributes to the risk of fractures.[101] It is prudent, therefore, that MS patients be monitored for bone density during the course of their disease, particularly in cases of inactivity and drug use that may compromise bone density.

Load-bearing exercise may stimulate maintenance of muscle mass sufficiently to slow the progression of sarcopenia in MS. Weight bearing during ambulation will also likely decrease the severity of lower-extremity osteopenia. We also recommend including resistance training to develop and maintain lean mass in the upper and lower body. Furthermore, increased awareness of the deleterious effects of MS on bone health through patient education and recommendations for a healthy diet and regular physical activity may attenuate the rate of bone loss.

4.4 Flexibility

Prevention of muscle contractures in the early stages of MS is highly encouraged. Stretching paretic muscles can prevent future painful contractures and reduce spasticity.[102] Slow and gentle stretching techniques are recommended. Flexibility exercises should be rhythmical, repetitive motion exercises with emphasis on improving motor control using proprioceptive facilitation techniques. Tight areas often involve muscles of the pelvis, chest, calf and hip flexors. Spasticity-aggravating factors such as pointing the toes during exercise should be avoided.

4.5 Systemic Fatigue

Several treatable medical conditions can underlie systemic fatigue, such as depression, thyroid disease and anaemia. Fatigue can also be an adverse effect of various medications or the result of muscle wasting. A comprehensive plan to treat fatigue, based on individual needs, is encouraged using the following options:

- occupational therapy to simplify tasks at work and home;
- patient education to learn energy-saving ways of walking (with or without assistive devices) and performing other daily tasks;
- establishing a safe and effective exercise programme;
- sleep regulation, which might involve treating other MS symptoms and using sleep medications on a short-term basis;
- psychological interventions, such as stress management, relaxation training, membership in a support group or psychotherapy;
- heat-management strategies to avoid overheating and ways to cool down.

4.6 Shortness of Breath

Respiratory muscles adapt to training programmes much like skeletal muscle.[79,103] O'Kroy and Coast[103] found that ventilatory muscle strength training in MS patients increased both maximal inspiratory and expiratory pressures. They also found that controlled breathing exercises increased respiratory muscle endurance.[103] The use of ventilatory resistive devices can help increase respiratory muscle strength.[79,103]

5. Recommendations for Fitness Evaluation in the MS Population

5.1 Aerobic Fitness Testing

Graded exercise testing provides the basis for individualised exercise prescription for enhancing cardiorespiratory fitness. The referring physician or other qualified clinician should perform a preliminary medical evaluation and clearance for exercise testing. Guidelines for the administration of exercise tests and prescription of exercise programmes in clinical populations are generally applicable to MS patients.[16,104] However, modifications to testing procedures and training programme design may be necessary to meet the needs of each patient and ensure safety.

The patient should be observed closely for signs of developing paresis or loss of coordination during

exercise. Since foot drop and other signs of paresis may develop with increasing exercise intensity, we recommend cycle ergometry as the preferred exercise testing mode. In addition, the use of toe straps may be helpful in clients with ankle clonus or sensory changes that alter coordination. Arm ergometry is suitable for non-ambulatory patients with adequate upper body function. We have found that treadmill testing is practical for higher functioning ambulatory patients.

The initial stage of exercise testing should provide a light warm-up; thereafter, the workload can be progressed in small incremental stages (10–25W), with each stage lasting 2–3 minutes to establish a steady state. Heart rate, blood pressure and the patient's perceived exertion should be monitored before exercise, during the steady state of each stage and in the immediate recovery period according to published guidelines.[16,104] Direct measurement of symptom-limited oxygen uptake or $\dot{V}O_{2peak}$ is recommended for assessment of functional aerobic capacity when equipment for respiratory gas analysis is available, but only if participant safety is not compromised by maximal exertion.

5.2 Heart Rate and Blood Pressure Response

In MS patients, the heart rate response to graded exercise testing is generally linear with respect to work rate, but it is blunted compared with healthy controls.[105] This attenuation of exercise heart rate may result from cardiovascular dysautonomia.[26,27,106] Unlike age-matched healthy individuals, many MS patients will experience fatigue, whether of central or peripheral origin, before attainment of their age-predicted maximum heart rate. Using the age-predicted maximum heart rate to estimate functional aerobic capacity will result in the actual percentage of $\dot{V}O_{2peak}$ utilised during exercise training being higher than indicated by the patient's actual heart rate. The actual heart rate response to graded exercise testing should be used, therefore, to prescribe the target heart rate range for training.

Similarly, cardiovascular dysautonomia is associated with an attenuated rise in blood pressure during exercise.[26,106] Inadequate rise in systolic pressure during exercise may lead to insufficient perfusion of the brain or muscles and the premature development of exertional symptoms such as lightheadedness or muscle fatigue. Caution should, therefore, be taken in both exercise testing and prescription to monitor heart rate and blood pressure in patients with suspected or known cardiovascular dysautonomia.

5.3 Muscle Strength and Endurance

Muscle strength in persons with MS is typically less than for healthy controls.[7,20,21,29,33,35,43] In addition, MS patients have a slower rate of muscle tension development[42] and reduced muscle endurance[37] (table I). Impairments in balance and motor control and the disability of each patient should be considered when evaluating muscle strength and endurance and prescribing a resistance training programme.

5.4 Flexibility

Flexibility is often compromised in MS patients, particularly in those with spasticity and, therefore, flexibility assessment should be conducted by an examiner with experience in range of motion testing in this population. We recommend assessment with a goniometer and performing flexibility exercises in the sitting or lying positions to increase the hold time of stretches and to reduce the risk of falling.

6. Recommendations for Exercise Prescription in MS

Individuals with MS should consult with their physician before starting a new exercise programme. The exercise programme should be designed with careful consideration of the capabilities or limitations of the patient, based on the results of preliminary exercise testing and the need to monitor MS symptoms. The exercise prescription should also include special consideration for specific patient goals. A physical therapist or clinical exercise physiologist experienced with the unique and varied symptoms of MS can help design or revise the exercise programme for patients who require supervision. In general, strenuous exercise should be avoided on days that the patient reports increased systemic fatigue.

Table V. General guidelines for aerobic exercise training

Frequency	Exercise intensity	Exercise duration
2–3 sessions/wk	65–75% HR_{peak}	20–30 min/session or 2 × 10–15 min/session
	50–70% $\dot{V}O_{2peak}$	
	RPE (11–14)	

HR_{peak} = highest value for heart rate found on symptom-limited exercise testing; **RPE** = rating of perceived exertion; **$\dot{V}O_{2peak}$** = highest value for oxygen uptake found on symptom-limited exercise testing.

6.1 Cardiorespiratory Exercise Training

MS patients have been shown to make favourable improvements in cardiorespiratory fitness in as a little as 4 weeks.[12] The exercise programme recommendations outlined below are based on the results of previous investigations and the American College of Sports Medicine guidelines for exercise testing and prescription[104] with modifications specific for MS based on our experience and others (table V).

Suggested modes of training to improve cardiorespiratory endurance include stationary cycling with legs and/or arms, swimming and aquatic exercise, although other exercise modes such as the treadmill or elliptical trainer may be suitable in high functioning MS patients. Barring symptoms that modify the prescription of intensity for aerobic training, the target zone can be individualised using a percentage of the observed peak exercise test heart rate or $\dot{V}O_{2peak}$, with consideration for the patient's rate of physical exertion in the target training zone. The original Borg scale of perceived exertion[104] ranges from 6 to 20 (6 = 'no exertion at all' and 20 = 'maximal exertion'). Ratings of 11–14 represent 'moderate intensity' and the ideal target intensity zone in the absence of symptoms.

Deficits in muscle strength may limit the ability of an MS patient to engage in aerobic exercise of sufficient intensity and duration to enhance cardiorespiratory fitness (White and Dressendorfer, unpublished observation). Progressive resistance exercise to improve muscle strength and endurance may, therefore, be necessary prior to aerobic training.

6.2 Alternating Bouts of Exercise with Rest Periods

Patients initially have low endurance capacity and require short rest periods during exercise sessions. Prescribing exercise on an intermittent basis helps to avoid excessive build-up of fatigue and heat stress, which worsen MS symptoms. Training benefits using this type of exercise-rest pattern are generally similar to the outcomes of continuous exercise for an equal duration.

6.3 Aquatic Exercise

Exercise in water temperatures of 27–29°C (80–84°F) may be advantageous for MS patients, particularly those who are heat sensitive or have high disability. One of the primary benefits of exercise in moderately cool water is that body heat is dissipated more easily than during land-based programmes. The thermal conductivity of water is about 25-times greater compared with air of a similar temperature.[107] Also, water reduces the effects of gravity and the buoyancy in water helps patients with weakened limbs attain a greater range of motion. In addition, chest-high water provides greater support, enabling many persons with MS to stand and maintain balance for exercises with less effort than on land. Wearing devices on the limbs to increase water resistance to movement can assist in muscle strengthening.[108]

Hydrotherapy incorporates specific techniques in water that can be utilised to decrease symptoms and address functional mobility deficits. Minimising elevations in core temperature with exercise may reduce symptoms of overheating and heat-related pseudo exacerbations. Moderately cool water temperatures (27–29°C) are recommended to help dissipate body heat generated during exercise.[109] Although the gradient for heat loss is increased as water temperature decreases, temperatures <27°C are not recommended to avoid increasing spasticity.

The benefits of water for heat dissipation have been extended to the use of exercise pre-cooling to minimise changes in core temperature with exercise. For example, White et al.[34] found that MS patients pre-cooled by lower body immersion in 16–17°C water for 30 minutes had lower rectal temperature,

heart rate and exertion ratings following 30 minutes of exercise at 60% $\dot{V}O_{2peak}$ compared with control conditions. Also, pre-cooling improved fatigue scores and 7.6m (25ft) walk time. The role of pre-cooling in selected MS patients deserves further investigation.

6.4 Strength Training

The resistance-training programme should be individualised to provide gradual progression of resistance for improving muscle tone, strength and endurance as well as promoting balance between agonist/antagonist and bilateral muscle groups. We recommend using closed-kinetic chain resistance exercises through the available range of motion. Special consideration should be given to gradually improving a reduction in range of motion that has resulted from the loss of connective tissue elasticity.

Several types of resistance may be used for muscle loading, including elastic bands,[110] free weights, machine weights and pulley systems. The patient's disability level will generally influence the type of resistance used. Conventional weight machines may be suitable in high functioning MS patients, whereas elastic bands of variable resistance may be more appropriate for low functioning patients.[110] Like other fitness training, the frequency and intensity of resistance training will vary based on the patient's current exercise tolerance. Two or three strength training sessions per week that consist of one to three sets of 8–15 repetitions for each major muscle group targeted are recommended.

Resistance exercises should target the legs, back, shoulders, chest and arms with regard for any specific disabilities that preclude otherwise. Weight lifting in the seated position, typical of most weight machines, minimises the potential risk for falls using free weights. Individuals with proprioceptive deficits or poor coordination will require supervisor cueing or standby assistance.

The rate of overload progression should be addressed with caution and allow for full recovery between training sessions to prevent musculoskeletal overuse injuries. In our experience, the resistance can be safely increased by 2–5% when 15 repetitions are correctly performed in consecutive training sessions.[96] However, variability in fatigue from day-to-day will likely warrant flexibility in the resistance programme. In our experience, symptom exacerbations from elevated body temperature in heat-sensitive patients occur less often with strength training than aerobic exercise. Combined cardiorespiratory and resistance programmes should alternate training on separate days of the week,[16] with 24–48 hours of recovery between training sessions. In this manner, strength exercises will each typically be performed on the average of two times per week.

6.5 Flexibility Exercise

MS patients often have reduced range of motion, muscle tone, strength, endurance, postural control, postural alignment, soft-tissue alignment and soft tissue integrity. The typical goals of a flexibility programme in MS are to increase muscle length, joint mobility, counteract the effects of spasticity and improve posture and balance. Caution should be taken to ensure that flexibility exercises do not overstretch peripheral nerves.

The most effective flexibility protocol for improving range of motion in persons with MS is unclear. Burks and Johnson[111] suggest that stretching exercises should be performed at least once daily and include all major muscle groups, including the shoulders and hips. Repeated short periods of gentle stretching distributed throughout the day may be preferable to a single stretching session.[112] General guidelines for stretching are as follows:[16]

- general flexibility exercises should be performed daily for 10–15 minutes;
- stretching should be done before and after aerobic and resistance exercise sessions;
- stretches should include the upper- and lower-body muscle groups used in a workout;
- slow, gentle and prolonged stretches are recommended for tight muscle groups;
- stretches should be held for 20–60 seconds for maximum benefit;
- stretching should not be painful.

Spastic muscles should be targeted for gentle stretching before and after exercise sessions. Each specific stretch should develop slowly, without bouncing, to the end of the comfort range and held for 20–60 seconds.[113] If the patient needs assistance, stretches can be done with a partner, rope or

towel. Immobilised MS patients with spasticity can be passively stretched with the assistance of a therapist or trained person. Passive range of motion above the joint of a paralysed area is recommended.[112]

The patient with spasticity will require gentle stretching exercises specifically designed to reduce muscle tone. Complementary techniques such as progressive muscle relaxation, deep breathing, yoga and meditation may also be helpful. Higher functioning MS patients may also enhance their flexibility through participation in supervised yoga classes.[97,114] Light massage may be helpful, with precautions for osteoporosis or oedema. Physicians may prescribe anti-spasmodic medications to improve the flexibility of patients with hyperreflexia.

6.6 Special Considerations for Supervision of Exercising MS Patients

Special considerations include patients with balance and coordination problems as well as sensory and proprioceptive deficits that increase the risk of falling. These issues should be specifically addressed when designing and supervising exercise programmes in the MS population. MS patients, not uncommonly, experience a temporary worsening of their symptoms when the weather is warm or humid or they run a fever, sunbathe, become overheated from exercise, or take very hot showers or baths. For example, some patients notice blurring of vision when they become overheated. This phenomenon is known as Uhthoff's sign. These heat-related symptoms can result with only a slight elevation in core body temperature because higher temperature further impairs conduction velocity in demyelinated nerves. Fortunately, short-term mild heat stress seems to cause only temporary worsening of symptoms without observable residual impairment after normothermia is regained.

To maximise work capacity, exercise sessions should be scheduled to avoid the hotter times of the day or those times when the patient experiences greater fatigue, especially in heat-sensitive patients. Exercise sessions in the morning, when it is cooler and when body temperature is typically lower, may be more tolerable than in the afternoon. MS patients may also have a reduced sweating response, making them predisposed to heat stress.[44,115] Exercise tolerance may be better in the morning because fatigue tends to worsen throughout the day. Moreover, patients who experience bladder problems during exercise may voluntarily limit their fluid intake before and during exercise, which can further reduce sweating, heat loss and performance.

In consideration of individuals with compromised cognitive function, it is recommended that exercise programmes be written down for easy reference. Exercise tasks should be explained in simple terms, demonstrated and initially performed with minimal resistance. Individuals with cognitive impairments may require additional supervision during exercise to ensure their safety.

7. Conclusion

Disability in MS is associated with reduced strength and aerobic endurance, spasticity, impaired balance and systemic fatigue. The loss of functional capacity in MS is likely compromised by physical inactivity resulting from these clinical problems. This review highlights the role of individualised activity prescription in the multidisciplinary approach to MS disease management for restoring functional capacity. Although further research is indicated, prescription of exercise that enhances cardiorespiratory endurance, muscle strength, mobility and balance shows promise as an effective intervention strategy to minimise functional losses in persons with MS.

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