Progressive multiple sclerosis 2

Treatment of progressive multiple sclerosis: what works, what does not, and what is needed

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This is the second in a Series of three papers about progressive multiple sclerosis

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Disease-modifying drugs have mostly failed as treatments for progressive multiple sclerosis. Management of the disease therefore solely aims to minimise symptoms and, if possible, improve function. The degree to which this approach is based on empirical data derived from studies of progressive disease or whether treatment decisions are based on what is known about relapsing-remitting disease remains unclear. Symptoms rated as important by patients with multiple sclerosis include balance and mobility impairments, weakness, reduced cardiovascular fitness, ataxia, fatigue, bladder dysfunction, spasticity, pain, cognitive deficits, depression, and pseudobulbar affect; a comprehensive literature search shows a notable paucity of studies devoted solely to these symptoms in progressive multiple sclerosis, which translates to few proven therapeutic options in the clinic. A new strategy that can be used in future rehabilitation trials is therefore needed, with the adoption of approaches that look beyond single interventions to concurrent, potentially synergistic, treatments that maximise what remains of neural plasticity in patients with progressive multiple sclerosis.

Introduction

More than 20 years have passed since the introduction of the first disease-modifying treatment for multiple sclerosis, interferon beta-1b.[1] Since then, nine further treatments have been approved and entered the market. All these drugs are for relapsing-remitting multiple sclerosis (RRMS), apart from interferon beta-1b (Betaseron), which has also been approved for use in secondary progressive multiple sclerosis (SPMS), but does not delay disability progression.[2] Therefore, the half of patients with multiple sclerosis who have progressive disease have been left behind by the therapeutic bandwagon. This situation raises the question of how we can help patients with primary progressive multiple sclerosis (PPMS) and SPMS. Although research is ongoing to find a treatment that could halt further deterioration in a disease that has already entered a progressive stage, in the meantime patients and their clinicians only have symptomatic treatment options. As we will make clear in this Series paper, many treatments and strategies are available for a disease with such diverse symptoms. However, the degree to which existing therapeutic approaches are based on empirical data derived from clinical trials confined to patients with progressive disease remains unclear. A critical review of the evidence is therefore timely. In the absence of disease-modifying treatments, what works symptomatically and what does not take on an even greater salience.

To choose which symptoms to include in this Series paper, we noted the views of patients with multiple sclerosis who have rated their symptoms in their perceived order of importance.[3] We have also linked these symptoms to quality-of-life indices[4] and have added our opinions regarding symptom significance, based on our clinical experience. The result is a Series paper that encompasses treatments for the following multiple sclerosis-related health issues: balance and mobility impairment, weakness, reduced cardiovascular fitness, ataxia, fatigue, bladder dysfunction, spasticity, pain, cognitive deficits, depression, and pseudobulbar affect. Prevalence rates and a summary of treatment options for each symptom are shown in tables 1 and 2.[5–59] We will conclude with some thoughts and recommendations about how future rehabilitation studies should proceed, derived from an existing initiative: the multinational Progressive Multiple Sclerosis Alliance.[60]

	Frequency
Mobility impairment	80%[5–7]
Balance impairment	75%[8]
Weakness	70%[9]
Ataxia	80%[10,11]
Fatigue	80%[12]
Bladder dysfunction	58–75%[13,14]
Spasticity	60–90%[15]
Pain	55–70%[16]
Cognitive dysfunction	60–70%[17,18]
Depression	25–50%[19]
Pseudobulbar affect	10%[20]

Table 1: **Symptom frequency in progressive multiple sclerosis**

Balance and mobility impairment

Multiple sclerosis causes a wide range of neurological deficits, which often interact to cause mobility difficulties. Within 10–15 years of disease onset, 80% of patients have walking difficulties,[5–7] which is of major concern to people with the disorder who report mobility as their most valued bodily function.[3] An important contributor to mobility difficulties is impaired balance. Roughly 75% of people with multiple sclerosis report balance problems during the course of their disease,[8] even in the very early stages,[5] with more impairment in people with progressive forms of multiple sclerosis than

in those with RRMS.[61] Impaired balance is characterised by increased sway in quiet stance, delayed anticipatory and automatic postural adjustments, and reduced ability to move towards the limits of stability.[8] Poor balance performance on static and dynamic balance tests is associated with falls, with more than 50% of affected individuals falling within a 6-month period[62] and 29–45% prone to recurrent falls.[63] Importantly, people with multiple sclerosis have a twofold increased risk of fall-related injuries compared with healthy individuals,[64] and a fear of falling that can lead to a loss of confidence and restriction in activity levels.[65]

In view of the widespread and variable nature of CNS damage in multiple sclerosis, the cause of impaired balance and mobility is probably multifactorial and hypotheses about the key mechanisms vary. Some people believe that impaired central integration of visual, vestibular, and somatosensory input is key, whereas others suggest that the cerebellum could be the main contributor.[66] Cognitive resources are also needed for postural control, with more difficult postural tasks requiring greater cognitive processing than simpler tasks. A meta-analysis assessing risk factors associated with falls showed that a progressive disease course is associated with a twofold increased risk of falling compared with a relapsing-remitting disease course.[63]

A range of interventions aimed at enhancing balance in standing and walking are used in clinical practice, the most common of which is physiotherapy. A systematic review comprising 11 randomised controlled trials,[21] of which only one was restricted to progressive disease,[22] concluded that physiotherapy has small, but significant, beneficial effects on balance in those with mild to moderate disability, but evidence for the effects in severely disabled

	Trial type	Endpoint (primary/ secondary)	Benefit?	Multiple sclerosis disease course
Balance impairment				
Specific balance exercises	RCT	Primary	+	RRMS and progressive MS (not analysed separately)[21]
Physiotherapy exercises	RCT	Primary	+	RRMS and progressive MS (not analysed separately)[21]
Physiotherapy exercises	Pilot RCT	Secondary	±	PPMS and SPMS[22]
Mobility impairment				
Treadmill training	RCT	Primary	+	RRMS and progressive MS (not analysed separately);[23] SPMS[24]
Physiotherapy	RCT	Primary	+	RRMS and progressive MS (not analysed separately)[21]
Aerobic exercise training (eg, leg and/or arm cycle ergometry)	Pilot RCT	Secondary	+	SPMS[25]
Progressive resistance training	RCT	Secondary	±	RRMS and progressive MS (not analysed separately)[10,26]
Exercise training	RCT	Primary and secondary	±	RRMS and progressive MS (not analysed separately)[6]
Weakness				
Progressive resistance training	RCT	Primary	+	RRMS and progressive MS (not analysed separately)[26]
Physiotherapy exercises	RCT	Primary	+	RRMS and progressive MS (not analysed separately)[26]
Aerobic exercise training	RCT	Secondary	+	RRMS and progressive MS (not analysed separately)[26]
Locomotor training	RCT	Secondary	±	RRMS and progressive MS (not analysed separately)[26]
Cycle ergometry	RCT	Primary	+	RRMS and progressive MS (not analysed separately)[26]
Combination training (eg, cycle ergometry and pylometrics)	RCT	Primary	±	RRMS and progressive MS (not analysed separately)[26]
Reduced aerobic capacity				
Aerobic exercise training (eg, leg and/or arm cycle ergometry)	RCT	Primary	+	RRMS and progressive MS (not analysed separately)[26]
Aerobic exercise training (eg, leg and/or arm cycle ergometry)	Pilot RCT	Primary	±	SPMS[25]
Combined aerobic and resistance training	RCT	Primary	±	RRMS and progressive MS (not analysed separately)[26]
Ataxia				
Medication				
Isoniazid and pyridoxine	Crossover	Primary	±	RRMS and progressive MS (not analysed separately)[11]
Cannabinoids	RCT	Secondary	±	RRMS and progressive MS (not analysed separately)[27]
Surgical interventions				
Thalamotomy versus deep-brain stimulation	Comparative	Primary	±	RRMS and progressive MS (not analysed separately)[11]
Physiotherapy/rehabilitation	Comparative	Secondary	±	RRMS and progressive MS (not analysed separately)[28,29]

(Table 2 continues on next page)

	Trial type	Endpoint (primary/ secondary)	Benefit?	Multiple sclerosis disease course
(Continued from previous page)				
Fatigue				
Medication				
Amantadine	RCT	Primary	±	RRMS and progressive MS (not analysed separately)[30]
Carnitine	RCT	Primary	±	RRMS and progressive MS (not analysed separately)[31]
Energy conservation programme	RCT	Primary	±	RRMS and progressive MS (not analysed separately)[32]
Energy conservation programme	Crossover	Primary	±	SPMS[33]
Aerobic exercise training	RCT	Secondary	±	RRMS and progressive MS (not analysed separately)[26,34]
Aerobic exercise training	Pilot RCT	Secondary	±	SPMS[25]
Progressive resistance training	RCT	Secondary	±	RRMS and progressive MS (not analysed separately)[26]
Bladder dysfunction				
Botulinum toxin	RCT	Primary	+	Not specified[35]
Portable bladder ultrasound	Longitudinal	Primary	±	Not specified[36]
Percutaneous abdominal stimulation	RCT crossover	Primary	–	Not specified[37]
Pelvic floor muscle training and electrical stimulation	Longitudinal	Primary	–	Not specified[38]
Solifenacin	Longitudinal	Primary	+	Not specified[39]
Spasticity				
Botulinum toxin and physiotherapy	RCT	Primary	+	PPMS[40]
Sports climbing; yoga	RCT	Primary	–	RRMS and progressive MS (not analysed separately)[41]
Transcutaneous electrical stimulation	Crossover	Primary	–	Not specified[42]
Functional electrical stimulation cycling	Longitudinal	Secondary	–	PPMS and SPMS[43]
Naltrexone	Longitudinal	Secondary	+	PPMS[44]
Nabiximol	RCT	Primary	+	Not specified[27,45]
Pain				
Treadmill training, bodyweight-supported/ robot-assisted training	RCT	Secondary	+	PPMS and SPMS[46]
Transcutaneous electrical nerve stimulation	RCT	Primary and secondary	–	Not specified[47,48]
Exercise, massage	RCT	Primary	+	RRMS and progressive MS (not analysed separately)[49]
Vibration therapy and exercise	RCT	Secondary	+	Not specified[50]
Intrathecal baclofen and morphine	Retrospective	Primary	+	SPMS[51]
Nabiximol	RCT	Primary	+	Not specified[45]
Cognitive dysfunction				
Medication				
L-amphetamine	RCT	Primary	+	RRMS and progressive MS (not analysed separately)[52,53]
Donepezil	RCT	Primary	–	RRMS and progressive MS (not analysed separately)[54]
Cognitive retraining	RCT	Primary	+	RRMS and progressive MS (not analysed separately)[55]
Cognitive retraining	RCT	Primary	+	RRMS and progressive MS (not analysed separately)[56]
Exercise	RCT	Secondary	+	PPMS and SPMS[25]
Depression				
Medication				
Desipramine	RCT	Primary	±	Not specified[57]
Paroxetine	RCT	Primary	±	Not specified[57]
Cognitive behaviour therapy	RCT	Primary	+	RRMS and progressive MS (not analysed separately)[58]
Exercise	RCT	Secondary	+	PPMS and SPMS[25]
Pseudobulbar affect				
Medication				
Dextromethorphan plus quinidine	RCT	Primary	+	Not specified[59]

RCT=randomised controlled trial. RRMS=relapsing-remitting multiple sclerosis. MS=multiple sclerosis. PPMS=primary progressive multiple sclerosis. SPMS=secondary progressive multiple sclerosis. +=Yes. –=No. ±=Equivocal.

Table 2: **Studies of symptomatic management in chronic progressive multiple sclerosis**

people is scarce. A range of physiotherapy techniques were used in these trials, including specific balance exercises, neuromuscular facilitation, resistance training, and aerobic training, but their relative effectiveness is not known either for those with RRMS or progressive disease.

Neural plasticity is enhanced following task-specific rehabilitation.[67,68] Therefore, balance and mobility interventions are thought to provide the appropriate task-specific stimuli to help neural re-organisation of central sensory integration, thereby leading to improved stability (panel 1). Although greater benefits are generally believed to be gained from balance and mobility interventions in the earlier phases of multiple sclerosis, there is encouraging evidence that the capacity for neuroplasticity and motor learning seems to continue even in those with more severe disability.[68] For example, a systematic review of studies investigating the effect of treadmill or robot-assisted training provides modest evidence to show that improvements in quality of life and gait can occur in those patients with high levels of disability.[23] Of the eight studies included, two were small single-group studies that restricted their sample to patients with progressive disease.[24,69] However, whether or not there is a point at which neural reserve becomes too low for neural plasticity to promote functional change remains unknown. Peripheral physiological changes, such as muscle endurance, also contribute to changes in balance status. So too does the ageing process, in which reintegration of sensory information becomes more difficult and attention demanding for older adults. This situation has substantial relevance for people with progressive multiple sclerosis who are more likely to be older patients with a greater disability burden.

In summary, insufficient evidence exists to support balance or mobility retraining as effective interventions for people with progressive disease, although data from mixed patient samples are promising. Future research should establish whether or not those with progressive multiple sclerosis, and at different levels of disability, respond differently to these interventions, and if so whether and when interventions should be re-focused on compensatory rather than restorative strategies.

Weakness

Weakness is present in up to 70% of people with multiple sclerosis.[9] Reduced muscle strength seems to mainly affect the lower limbs, although weakness in the upper limbs, trunk, and respiratory muscles is also problematic.[10,70,71] Muscle strength is important since it is associated with mobility difficulties (reduced gait speed and endurance), balance, and functional activities.[72] The relative contribution of the disease process and reduced physical activity levels to weakness remains unclear; it might differ substantially between disease phenotypes and needs further investigation.

Physical therapy interventions, such as resistance training and task-specific training, are the mainstay of interventions. A systematic review and meta-analysis[10] provides strong evidence in support of the use of resistance training (eg, weight machines, free weights, and resistance bands) to improve lower limb strength, although the evidence for its effect on upper limb strength and mobility, functional capacity, and balance is modest. Other forms of strength training (eg, locomotor training, cycling, and aquatics) can also enhance lower limb strength.[26] Small but clinically meaningful improvements in walking mobility for mixed disease types have been shown by a systematic review and meta-analysis of 22 published studies investigating exercise training, although no significant effect was recorded in the groups composed solely of people with progressive disease.[6] However, the authors emphasise that this finding might be indicative of the small number of studies (ie, four)

Panel 1: Case study 1—physical rehabilitation

A 50-year-old man with a 25-year history of multiple sclerosis that had entered a secondary progressive phase 15 years previously was referred after being admitted to hospital because of frequency of micturition, confusion, and hallucinations. Symptoms were attributed to pyelonephritis and antibiotics initiated. His history showed that he had been wheelchair bound for the past 12 years, but had managed to live alone at home in an adapted flat with assistance and support from social services and his adult children when it came to shopping and housework. However, in the past 12 months his physical condition had started to deteriorate and he was struggling to maintain independence in many self-care activities.

Unable to return home with his existing level of function, he was transferred to a rehabilitation unit where he was assessed as being dependent for all self-care, transfers, and mobility. Physical examination showed spastic paraparesis, trunk and upper limb weakness, poor sitting balance, bladder hyper-reflexia with urinary tract infection, constipation, pressure sore on the right heel, changed sensation in the lower limbs, low activity tolerance, cognitive impairment, depression, and fatigue. He scored 8·0 on the Expanded Disability Status Scale and subjectively rated his quality of life as poor. Working with the patient, his rehabilitation team established a set of goals that included returning home with minimum assistance for self-care and domestic tasks, independence in transfers and in performing a home exercise programme, and improved bladder, bowel, and muscle tone management.

To achieve these goals, an intensive multi-disciplinary programme was started that involved re-education with respect to self-care and domestic activities, transfers and sitting balance, pressure care, and prevention and treatment of urinary tract infections, which included self-medication. A regimen of suppositories and regular aperients was started and advice given for continuation post-discharge. Following a psychiatric assessment, anti-depressant treatment was started, and simple, basic training provided in relaxation techniques to cope with anxiety and stress. A meeting was also held with the patient and his caregivers and family to provide education pertaining to cognitive compensatory strategies to offset, in part, his memory dysfunction. Finally, referrals were made to a local wheelchair service for wheelchair adaptations and a pressure-relieving cushion, and to community services for home modifications that included rails to be fitted beside the toilet and the installation of an intercom system.

After 4 weeks of inpatient rehabilitation, the patient was discharged home because he had achieved his short and intermediate goals of improving functional independence and quality of life. Close liaison with community services was judged to be crucial to ensure safety in the home and the carryover and sustainability of the many improvements gained.

focused on progressive disease, rather than a true differential effect of exercise training, and conclude that further research is needed in this disease subtype before recommendations can be made.[6]

Preliminary research suggests that exercise might delay disease progression by reducing inflammation and encouraging neuronal repair. In view of the fact that exercise studies done so far typically comprise samples of mixed disease types, a pressing need exists to focus on progressive disease since many of the issues related to deconditioning might be especially pertinent to this phenotype.

Weakness in multiple sclerosis was, until fairly recently, not thought to be amenable to drug treatment.[7] However, a recent Cochrane review of 4-aminopyridine shows that, in a subset of patients, this well tolerated drug improved walking speed and muscle strength of the lower extremities.[73] In-vitro studies suggest that the likely mechanism of action is improved impulse conduction through demyelinated lesions.[73] Of 16 clinical studies of 4-aminopyridine, only one restricted sample selection to people with progressive disease and this study did not measure muscle strength or mobility.[74] Therefore, at present, no recommendations can be made for those with progressive disease in relation to the effect of 4-aminopyridine on weakness or mobility.

In summary, an absence of clinical trials in people with progressive disease means that insufficient evidence currently exists to support either medication or resistance training as effective interventions for improving mobility, functional capacity, or upper limb strength in people with progressive multiple sclerosis. Existing evidence supports the use of progressive resistance training to improve lower limb strength, but replication studies are needed to confirm this idea.

Reduced cardiovascular fitness

Compared with people with other chronic diseases, individuals with multiple sclerosis are at the lowest end of the physical activity scale (ie, they do the least amount of physical activity).[75] A meta-analysis provides strong evidence that aerobic exercise training, such as cycle ergometry, undertaken at least two to three times per week for 30–60 min at a moderate intensity can effectively improve aerobic capacity and power output in people with mild to moderate disability.[26] Most of these studies include both RRMS and progressive disease, so whether those with progressive multiple sclerosis, or severe disability, also benefit remains uncertain. Encouragingly, evidence from recent small-scale exercise studies of people with progressive multiple sclerosis, with moderate and severe disability, suggests that endurance training can improve aerobic capacity,[25,76] leading to an increase in walking distance.[25] Low dropout rates and good levels of adherence also provide cautious optimism that this intervention is feasible and acceptable in those with progressive disease.[77] Further research is needed to confirm these findings.

In summary, evidence is accumulating to support the effectiveness of aerobic exercise training in people with progressive disease. However, so far the studies are too few and lack the methodological rigor to inform clinical practice.

Ataxia

An estimated 80% of patients with multiple sclerosis experience ataxia at some point in their disease course.[10,11] A range of treatments are available, including pharmacotherapy (eg, isoniazid, pyridoxine, and cannabis), stereotactic neurosurgery (thalamotomy or deep-brain stimulation), and neurorehabilitation. However, treatment remains challenging. The only Cochrane review that has focused specifically on ataxia in multiple sclerosis concluded that insufficient evidence exists for the efficacy and tolerability of pharmacotherapies to treat this aspect of the disease.[11] This is also the case for neurosurgery and neurorehabilitation, despite the occasional promising result.[28,29] Moreover, no studies have focused on progressive multiple sclerosis.

Treatments for ataxia can be broadly divided into those that are compensatory and those that are restorative in nature. Compensatory approaches involve teaching individuals how best to manage their ataxia. A range of strategies include the following: decomposition of movement into simpler single joint movements; visual and verbal cues to help walking speed and stride length; biofeedback through virtual reality or electromyography; and aids to help posture, balance, and mobility. Lycra garments have also been used to improve trunk stability and function, although only preliminary evidence regarding their effectiveness exists at present.[78] Interventions that increase inertia by loading the limbs or trunk with weights have shown varied success.[28] Cooling of a limb can also temporarily reduce cerebellar tremor by increasing muscle stiffness or reducing any one or more of muscle thixotropy, nerve conduction velocity, and muscle spindle afferent feedback.[28]

Evidence supporting the effectiveness of restorative approaches is moderate at best. Biofeedback, such as that linked to computer games that require balance and multi-segment coordination, has proved helpful in some patients to improve balance and falls.[79] Other studies have assessed the effect of multicomponent approaches on balance and walking, such as balance activities combined with ocular exercises,[80] or a combination of conventional physiotherapy strength and balance exercises.[22] Small-scale studies of adaptive robot therapy (that enables highly repetitive, intensive, and interactive activity) have shown some success in improving manual dexterity and coordination of the upper limbs, indicating that patients can adapt by learning to predict the effects of perturbing forces.[81] More recently, studies have explored the use of rapid transcranial magnetic stimulation (motor cortical stimulation), and have demonstrated an improvement in hand function

compared with controls.[82] The mechanisms underlying these improvements remain unclear.

In summary, recommendations about the management of ataxia in people with progressive multiple sclerosis cannot be made because of insufficient research into this topic.

Fatigue

Fatigue occurs in up to 80% of patients with multiple sclerosis and is reported more frequently in progressive than in relapsing-remitting disease.[12] It is an important determinant of quality of life, with two-thirds of patients reporting fatigue as one of their most troubling symptoms.[83] Effective treatment remains scarce. Although several strategies are routinely used in clinical practice, treatment recommendations are based on very little scientific evidence. Systematic reviews provide some evidence in favour of drug therapies and energy conservation treatment, although studies have yielded mixed results.[30–32] Results from a randomised controlled trial, and confirmed in a meta-analysis (albeit with a mixed disease type), support the potential benefits of exercise on fatigue.[34,84] Randomised controlled trials of vestibular rehabilitation and patient education programmes that incorporate a cognitive behavioural approach also provide some evidence of benefit,[85–87] as have some,[88] but not other,[89] multifaceted rehabilitation studies. Although small-scale studies of energy conservation techniques or exercise focusing solely on people with progressive multiple sclerosis have been undertaken,[25,33] these are rare and typically assess only short-term outcomes. Caution should therefore be taken in the extrapolation of conclusions to this phenotype.

Successful treatment of fatigue with use of behavioural approaches is increasingly recognised to possibly affect the underlying biology. Therefore, future studies, in addition to focusing on progressive disease, should incorporate biomarkers to elucidate the potential mechanisms underpinning any observed behavioural changes.[90] This approach has been used to a limited extent in patients with RRMS.[91,92] Patients with subjective fatigue were given single doses of rivastigmine and 3–4 diaminopyridine, with resultant improvements in brain activation patterns associated with information processing speed and motor activity, respectively.[91,92]

In summary, although some evidence supports the effectiveness of drug therapies and behavioural approaches such as energy conservation treatments in mixed patient samples, this finding has yet to be confirmed in patients with progressive disease.

Bladder dysfunction

Most people with multiple sclerosis experience bladder problems during their lives.[13,14] These difficulties correlate highly with quality of life. Although moderate to severe bladder and bowel problems are common even in patients with a relatively recent diagnosis,[93] studies do not generally distinguish between disease types when it comes to the frequency and severity of symptoms.

A reduction in the frequency of incontinence is important from a psychological and self-esteem perspective. In initial stages of bladder overactivity, pharmacological agents such as anticholinergics (eg, oxybutynin) and antimuscarinic agents (eg, solifenacin) are typically used.[39] More recently, botulinum toxin injections have received US Food and Drug Administration approval for the treatment of urinary incontinence resulting from detrusor overactivity caused by multiple sclerosis. The study with the largest enrolment of participants with multiple sclerosis (n=154) did not provide information about disease course,[35] but a smaller study of 43 patients did, although without providing a breakdown of the proportion of participants with RRMS, PPMS, and SPMS.[94] Both these studies reported improvements in urinary incontinence with botulinum toxin treatment.

Depending on severity, rehabilitative methods such as facilitated emptying through intermittent catheterisation or external compression are the approaches typically recommended for the management of neurogenic bladder. Assistive devices have been assessed to direct the timing of catheterisation, which is usually based on symptoms, post-void residuals, or a set schedule. Portable bladder ultrasound devices, which allow switching from a time-dependent to a volume-based catheterisation, have been shown to significantly reduce frequency of incontinence.[36]

The most frequently used method to assist bladder emptying is suprapubic bladder compression. This approach can be an alternative to intermittent catheterisation if residual volumes are sufficiently reduced, or if intermittent catheterisation is difficult because of other impairments such as problems with fine dexterity. A randomised controlled trial in patients with multiple sclerosis showed that, compared with no treatment, percutaneous stimulation (vibration) applied to the suprapubic region of the abdomen was effective in reducing residual volumes, but no effect was reported for abdominal pressure alone.[37] Furthermore, despite the significant improvement in post-void residual volume, the frequency of micturition or incontinence did not change.

Pelvic floor rehabilitation for stress incontinence is one of the few rehabilitative training methods for bladder dysfunction in multiple sclerosis. A study of pelvic training using electrical stimulation and biofeedback for ten 30-min sessions reported better muscle strength and reduced frequency of incontinence with this approach.[38] However, despite improvement in the functional capacities of the bladder, residual volumes did not significantly improve, which suggests that this therapy is best indicated for those with mild multiple sclerosis, without pelvic floor spasticity or detrusor sphincter dyssynergia. Once again, studies are few, and they have restricted their recruitment to those with RRMS.

In summary, no treatment studies have focused exclusively on progressive multiple sclerosis patients with bladder dysfunction. As such, the effectiveness of the treatments and approaches summarised in this section remains unclear for people with progressive disease.

Spasticity

Spasticity in multiple sclerosis is a manifestation of disrupted descending motor pathways caused by axonal degeneration or demyelination. Around 60–90% of people with multiple sclerosis will develop spasticity during their lifetime.[15] Spasticity can be localised, multifocal, or regional, and can add to impairment by reducing the range of movement across joints, increasing stiffness, and contributing to pain, contractures, and pressure sores (panel 1). Spasticity curtails social participation and reduces quality of life.[15]

Treatment approaches are often multidimensional and include oral pharmacological agents, invasive and surgical procedures, and various rehabilitative therapies.[95] A Cochrane review discussed the use of various pharmacological agents for multiple sclerosis, including baclofen, diazepam, dantrolene, and tizanidine (among others), but reported no specific findings related to spasticity in progressive multiple sclerosis.[96]

A 6-month open-label study showed low-dose naltrexone effectively reduced spasticity in 40 patients with PPMS.[44] A study that included 38 patients with SPMS showed that 15 sessions of physiotherapy in addition to botulinum toxin type A injection had superior effects to botulinum toxin alone.[40] Another trial of patients with RRMS and SPMS compared the effects of two forms of aerobic physical activity—sports climbing and yoga—on spasticity.[41] No significant effects on spasticity were recorded after 10 weeks, although yoga improved cognition and sports climbing lessened fatigue. Results from a range of neurostimulation techniques, used alone or in combination with other interventions, are more promising. For example, transcutaneous electrical stimulation applied for 8 h was more effective than was a 60-min treatment at reducing spasticity,[42] and combination trials testing 2 weeks of intermittent transcranial magnetic theta burst stimulation plus exercise therapy decreased spasticity to a greater magnitude than did magnetic theta burst stimulation alone.[97] In a study confined to five patients with PPMS or SPMS, 6 months of home-based functional electrical stimulation cycling (in which electrical pulses prompt the legs to "cycle" on an adapted, stationary, recumbent bicycle) did not reduce lower extremity spasticity, although the specific stimulated muscle groups did increase in strength.[43]

Patients with spasticity have looked to cannabis for relief. Cannabis contains more than 60 cannabinoids, of which tetrahydrocannabinol (which has psychoactive properties) and cannabidiol are the most abundant. Two forms of pharmaceutically manufactured cannabis are used by patients with multiple sclerosis, namely a mucosal spray (nabiximol [Sativex]) and pills (dronabinol [Marinol] and nabilone [Cesamet]). Another option is the garden-grown variety (which can be legal or illegal, depending on country or state of residence), which is smoked or, less frequently, ingested. Uncertainty surrounds the putative benefits of cannabis. A randomised controlled trial of 572 patients with multiple sclerosis with refractory spasticity showed significant add-on benefits with nabiximol.[45] In a study design that was thought to replicate clinical practice, only those patients who had an initial reduction in spasticity of greater than 20% with nabiximol proceeded to the randomisation phase. Disease course was not specified, but a mean Expanded Disability Status Scale score of 6·0 in study participants suggests that many of them had progressive disease. Nabiximol is licensed for the treatment of multiple sclerosis-related spasticity throughout Europe, Canada, and the USA. Notwithstanding these developments, a recent American Academy of Neurology critical review concluded that subjective improvements in spasticity with nabiximol were probably not matched by the objective data.[27] The review also failed to find data to support the efficacy of smoked cannabis.[27]

In summary, the existing data from a small number of patients with progressive multiple sclerosis indicate that the addition of physiotherapy to botulinum toxin is superior to botulinum toxin treatment alone; home functional electrical stimulation cycling did not seem to be effective at reducing spasticity; no supporting data exist for the use of neurostimulation to reduce spasticity in the population with progressive multiple sclerosis; and opinions with respect to the efficacy of nabiximol are divided, in the context of no specific data for progressive multiple sclerosis.

Pain

A recent large systematic review[16] of 28 prospective studies with 7101 participants indicated a pooled pain prevalence of 62·8%. Prevalence according to disease type was as follows: SPMS 69·8%, PPMS 70·3%, and RRMS 50%. Headache was the most common type of pain (42%), followed by extremity pain (26·6%), back pain (20%), painful spasms (15%), Lhermitte's sign (16·6%), and trigeminal neuralgia (3·8%).[16] Pain, when present, is rated by patients as one of their most challenging symptoms. It is associated with a poor quality of life and interferes with daily activities, especially as its severity increases.[98,99]

Treatment for pain is very much pharmacologically based. Pain medications can account for nearly 30% of all drug use for all multiple sclerosis symptoms,[100] but patient satisfaction with their pain management is generally low.[99] Nabiximol (Sativex) is judged to be effective by an American Academy of Neurology review committee, although there was no comment in relation to a particular disease course.[27] Other medications shown

to be helpful for pain relief in multiple sclerosis (subtype not specified) are antidepressants, antiepileptic agents, opioids, and baclofen.[51] Medication treatment trials in progressive multiple sclerosis are scarce, but in one study of SPMS, intrathecal baclofen and morphine were reportedly effective.[101]

Few rehabilitation studies of pain mention progressive disease; among those that do are treadmill training studies. A quality-of-life analysis of 13 patients with PPMS or SPMS who had undergone bodyweight-supported treadmill or robot-assisted gait training showed that both training interventions resulted in significant longitudinal improvements in pain.[46] A randomised controlled trial for back pain assessed the use of high-frequency (110 Hz) and low-frequency (4 Hz) transcutaneous electrical nerve stimulation in 90 people with multiple sclerosis in which there was an inference of progressive disease without disease types being specified. The treatment was self-administered twice daily for 45 min per day, for 6 weeks.[47] The most notable reduction in pain was recorded in the high-frequency group. Similarly, 100 Hz transcutaneous electrical nerve stimulation has proven to be effective in reducing lower extremity pain following 8 h of stimulation in a group of patients in which disease type was not recorded.[48]

Exercise and massage are widely available interventions and a randomised study[49] compared exercise (strength, stretching, endurance, and balance) versus standard massage. The data showed that massage alone or in combination with exercise resulted in significant reductions in pain compared with exercise alone.[49] Similarly, whole-body vibration therapy combined with exercise proved more effective than exercise alone in reducing pain secondary to spasm.[50] Neither of these studies made reference to differential effects according to disease type.

In summary, data about rehabilitative interventions for pain in progressive forms of multiple sclerosis are scarce. Positive findings indicate that bodyweight-supported treadmill training can reduce pain. Although data from transcutaneous electrical nerve stimulation and exercise or massage studies also indicate beneficial effects, these findings have not been broken down according to disease type. The same limitations pertain to medication, with the exception of nabiximol and intrathecal baclofen with morphine.

Cognitive dysfunction

The prevalence of cognitive dysfunction varies from roughly 40% in RRMS to 60% in SPMS. Rates of dysfunction are higher in SPMS than in PPMS, whereas patients with RRMS have the lowest levels of impairment.[17,18] The cognitive domains affected most frequently are those of information processing speed, memory, and executive function. MRI data show that as the disease progresses, the neural networks that underpin cognition become more disorganised.[102] Excessive and more widespread recruitment of brain regions in SPMS indicate a failure of brain compensatory mechanisms and translate into greater cognitive dysfunction.[102] Of particular interest are findings from resting state functional MRI in which dysfunction in the anterior components of the default mode network were recorded in patients with SPMS and PPMS relative to healthy controls.[103] In turn, this dysfunction was also associated with more extensive cognitive decline. Yet although disease course predicts cognitive dysfunction, it cannot alone explain why cognition fails in some patients with progressive disease but not others. Here, the importance of cognitive reserve emerges; even in SPMS a lifetime of intellectual enrichment defined according to educational attainment and breadth of vocabulary mitigates, and in some cases prevents, cognitive decline.[104]

The ability of patients with multiple sclerosis to obtain and maintain employment, manage relationships, and complete everyday tasks is associated with their cognitive abilities (panel 2).[105] In view of the widespread, real-world functional implications of impairment, it follows that cognitive abilities are a major determinant of response to rehabilitation.[106] In a telling example of how apparently diverse functional abilities are intertwined, in-patient, individualised multidisciplinary treatment led to significant improvements in patient mobility, but only in those without severe cognitive impairment.[106]

The pharmacological treatment of cognitive dysfunction in multiple sclerosis has yielded mixed results. Although negative studies predominate, a few tentative successes have been reported. Disease-modifying therapies have proved disappointing, notwithstanding their ability to bring about improvement in brain MRI metrics. A trial of interferon beta-1b in 217 patients with SPMS and moderate disability used a single cognitive measure, namely the 3.0 second Paced Auditory Serial Addition test, for which a trend towards improvement was noted over the course of 36 months in the treatment group, but not the placebo group.[107] A double-blind, randomised, placebo-controlled trial of interferon beta-1b also did not offer any cognitive benefits to 73 patients with PPMS who were assessed over a 2-year period.[108] More promising results have, however, been obtained from putative cognitive-enhancing agents in studies that focused on specific cognitive domains in patients with multiple sclerosis who were defined as impaired at study entry. Benefits have been reported from randomised controlled trials with a single dose of methylphenidate,[109] 4 months of modafinil,[110] and L-amphetamine either given over 4 weeks or as four single doses.[52,53] What makes the L-amphetamine result more intriguing is that a drug that ostensibly targets attention was found to have more widespread effects that included improvements in both verbal and visuospatial memory. However, no such benefits were reported with the memory-enhancing agent donepezil.[54]

***Panel 2:* Case study 2—cognitive dysfunction**

A 42-year-old married man with three young children and a 5-year history of primary progressive multiple sclerosis, with a current Expanded Disability Status Scale score of 5·5, presented with a report of work-related problems. He had always taken his intellectual abilities for granted, having done well at university and thereafter progressed rapidly up the corporate ladder. However, he now reported that tasks that he had always taken for granted were taking much longer to complete, which meant having to take work home in the evenings and on weekends. As a result, he now had less time to spend with his wife and children, leading to a strained home life. Adding to his worries was the appearance of small work-related errors that had come to the attention of the company's senior management, who had called him in to express their concerns. Psychiatric inquiry ruled out the presence of a major depression, and a Mini Mental State Examination score was 29 out of 30, the one point lost for delayed verbal recall. In view of the primary cognitive nature of the patient's complaints, he was referred for neuropsychological assessment. The results showed superior premorbid intelligence and a generally intact cognitive profile, apart from indices of information processing speed and working memory in the borderline-normal range. Notwithstanding the absence of failure on any one cognitive test, these results suggested substantial cognitive decline, albeit mitigated by good cognitive reserve. This fall-off in function was judged to be sufficient to compromise the patient's ability to manage his intellectually challenging, fast-paced job. A trial of donepezil treatment failed to bring about improvement. A combination of methylphenidate and 12 weeks of cognitive retraining produced modest benefits only marginally improving work performance. At that point, with the patient's consent, his company was approached with a recommendation for worksite accommodations, in particular a reduced workload, more time to complete tasks, and a maximum 36-h working week. The company agreed to a 6-month trial period that proved successful. It was then agreed between all parties that the situation would be reviewed annually.

Recent results have suggested that cognitive retraining might, despite receiving negative to lukewarm Cochrane reviews, hold promise (panel 2).[111] Reasons for this new-found enthusiasm include modifications to the type of retraining offered, a willingness to look beyond randomised controlled trials to different approaches such as a controlled within-participant study design, and the ability to show changes in cerebral activation on functional MRI commensurate with the cognitive improvements. One study that holds particular promise for patients with progressive multiple sclerosis involved a mixed group of participants (17 with RRMS, four with PPMS, and seven with SPMS); the greatest benefit derived from the use of context and imagery to improve new learning was found in participants who had more severe impairments to start with.[55] The same group went on to replicate this result in a larger randomised controlled trial of 86 patients with multiple sclerosis. Of the 45 participants in the active treatment group, eight had progressive disease (one PPMS, six SPMS, and one progressive relapsing).[56] Although no specific treatment group interaction was sought or reported in either of these studies, in view of what is known about memory impairment across the range of disease course, the assumption that benefits accrued to many of the patients with progressive disease is reasonable. The same conclusions could be inferred from a study that also focused on memory deficits, but included functional MRI correlates obtained before and after cognitive retraining. Improvements in memory were linked to increased cerebral activation during performance of a cognitive task, but only in the eight participants who had received treatment, three of whom had progressive multiple sclerosis (no further subdivision was provided).[112] However, the positive interpretation of findings like these cannot obscure the fact that much remains unknown. As with the medication trials, the data are heavily skewed towards patients with RRMS and even here, it is unclear how long benefits remain following treatment cessation or the degree to which improvement on one cognitive measure translates into enhanced day-to-day functioning.

Improvements in cognition, or a halt to the progression of cognitive decline, depend on the degree to which brain plasticity has been compromised. Here, as the functional brain imaging data show, patients with progressive multiple sclerosis—especially SPMS—are affected to a greater extent than are those with RRMS. However, some tentative evidence suggests that cerebral compensatory mechanisms even in these patients remain viable and receptive to therapeutic interventions. The first piece of supporting evidence comes from the cognitive reserve literature. If intellectual enrichment can prevent or delay the onset of cognitive decline, might not an intervention that promotes a more cognitively stimulating lifestyle halt or even reverse the deficits that are already apparent? Although the answer to this question is not yet known in progressive multiple sclerosis, what is more certain is that increased physical activity carries the promise of cognitive benefits. In a randomised controlled trial of 42 patients with progressive multiple sclerosis (31 SPMS and 11 PPMS) with moderate physical disability (Expanded Disability Status Scale score 4–6) significant improvements in aerobic fitness and several secondary outcome measures, including indices of cognition, were noted in those patients assigned to various forms of exercise rather than a waitlist group.[25] The study was notable for being the first that specifically targeted physical function and cognition in patients with progressive multiple sclerosis.

In summary, insufficient evidence currently exists to support medication or cognitive retraining as effective treatments for cognitive impairment in progressive multiple sclerosis (panel 2), although promising data for cognitive retraining in mixed samples of patients with multiple sclerosis are duly noted. Exercise seems to benefit cognition, but replication studies are needed and the best type of exercise needs to be clarified.

Depression

Between a third and half of all patients with multiple sclerosis will develop major depression during the course of their lives.[19] Unlike cognition, however, the association with disease course is equivocal.[113,114] What this uncertainty indicates is that the underlying cause of depression is

complex, with explanations less reductionist than those used to explain cognitive dysfunction. The findings from brain imaging are nonetheless informative and account for around 40% of the variance in explaining the presence of depression.[115] A similar percentage has been reported for a miscellany of psychosocial factors.[116] The deleterious effects of depression on patients with multiple sclerosis are substantial (panel 3). Not only is it associated with an increased suicide rate compared with that in the general population,[117] but it is also a major determinant of quality of life.[118] Therefore, the fact that depression is often overlooked in neurological clinics and, even when detected, inadequately treated, is worrying.[119] Recently published treatment guidelines from the American Academy of Neurology, however, draw attention to the dearth of empirical data to guide treatment decisions.[59] A Cochrane review of antidepressant medication for multiple sclerosis-related depression noted modest benefits and prominent side-effects.[57] A second Cochrane review that focused on various forms of psychotherapy for patients with multiple sclerosis was more enthusiastic about cognitive behavioural therapy.[58] The American Academy of Neurology also cautiously endorsed cognitive behavioural therapy, even when given over the telephone (panel 3)—a finding that has practical implications for patients with progressive multiple sclerosis whose high degree of neurological impairment can prove a barrier to attending regular clinic-based treatment.[59] Unfortunately, this piece of logistical good news does not necessarily make cognitive behavioural therapy an effective treatment of choice for depressed patients with progressive multiple sclerosis. As is the case for published studies on cognitive rehabilitation, the findings are again weighted appreciably in favour of individuals with RRMS. It th`erefore remains unclear whether cognitive dysfunction, which is more frequent and extensive in progressive multiple sclerosis, presents an obstacle to cognitive behavioural therapy, if not an insuperable barrier. Finally, although the exercise treatment data for multiple sclerosis-related depression are generally mixed,[120] the one study that limited enrolment to patients with SPMS reported an improvement in mood as one of the secondary outcome measures.[25]

In summary, although cognitive behavioural therapy is an effective treatment for depression in multiple sclerosis, it is premature to conclude that the benefits apply to patients with progressive disease. No firm conclusions can be drawn in relation to antidepressants and exercise as effective treatments in progressive disease.

Pseudobulbar affect

Pseudobulbar affect (pathological laughing and crying), which is present in up to 10% of patients with multiple sclerosis, mainly occurrs in patients with SPMS.[20] Treatment guidelines suffer less from the equivocation that bedevils cognition and depression. A combination of dextromethorphan and quinidine is endorsed in the American Academy of Neurology's recommendations.[59]

In summary, dextromethorphan with quinidine is likely to be an effective treatment for pseudobulbar affect in progressive multiple sclerosis.

Conclusions

When the focus falls on progressive multiple sclerosis, the designation of disease course can prove challenging, especially for defining the point at which RRMS transitions into SPMS. All studies of progressive multiple sclerosis confront this problem and our Series paper is no exception. With this potential limitation in mind, some common threads run through our review of symptomatic treatment studies for progressive multiple sclerosis. The main finding to emerge is that studies devoted solely to patients with SPMS or PPMS are scarce (table 2). Furthermore, when patients with progressive disease are included alongside those with RRMS, the number of patients is usually very small and analysis of

Panel 3: Case study 3—depression

A 34-year-old married woman with a 12-year history of multiple sclerosis that had entered a secondary progressive phase 5 years ago was referred for psychiatric assessment because of low mood. Her Expanded Disability Status Scale score was 5·0 and she needed a walker to walk because of increasingly poor balance. Her history showed she had to stop working because of her tremor and increasingly frequent falls. She dated her low mood from this time. In addition to experiencing persistent sadness, she reported a loss of enjoyment of life, early morning waking, loss of interest in sex, what she called "comfort eating" with a 10 lb weight gain, a sense of frustration at finding herself at home alone while all her friends were working, and a dip in self-esteem, but no suicidal thoughts. She was diagnosed with major depression and offered a choice of two treatments: either antidepressant medication or cognitive behavioural therapy. She chose antidepressant medication because she viewed it as the simpler of the options and one that did not need weekly therapy sessions. One month after starting 20 mg citalopram once daily, a selective serotonin reuptake inhibitor, she returned for psychiatric follow-up. Her mood was reported to be marginally better and sleep had improved, but dry mouth, constipation, and low-grade nausea were troubling side-effects. A decision was made to stay with the treatment with the expectation that side-effects would diminish with time. By her 2-month follow-up, some further improvements in mood and sleep had occurred, but the nausea had become too unpleasant to tolerate and although this had the unforeseen effect of reducing appetite with concomitant weight loss, she requested that the medication be stopped. The patient was then offered a switch to mirtazepine, a noradrenergic and specific serotonin reuptake inhibitor with few gastrointestinal side-effects. However, after weighing up the benefits of treatment, which also included a low prevalence of sexual side-effects, against potential adverse reactions such as sedation and increased appetite, the patient decided to try cognitive behavioural therapy instead. Since she lived some distance away from the clinic and was unable to drive because of her multiple sclerosis, she would have had difficulty managing the weekly cognitive behavioural therapy clinic appointments, the therapy was offered over the telephone. After a 12-week course of treatment, her mood was substantially better and the medication side-effects had abated. A 6-month follow-up visit showed that mood remained largely euthymic. Bouts of despondency, although still present, were infrequent and short lived, resolving within hours. The patient had regained her libido and was planning on becoming more involved in community activities.

Search strategy and selection criteria

For this Series paper, we identified references through searches of PubMed and MEDLINE. Search terms were "progressive multiple sclerosis", "secondary progressive", "primary progressive", "symptom management", and "progressive multiple sclerosis rehabilitation". The period covered was Jan 1, 1994, until Jan 31, 2014. Articles were also identified through searches of the reference lists of the articles found (using the same aforementioned cited search terms) and of the authors' own files. We gave preference to randomised controlled trials. We reviewed only papers published in English. The final reference list was generated on the basis of originality and relevance to the scope of this Series paper.

treatment effects does not take into account the possible effect of disease course. Finally, in those few studies in which benefits of treatment are noted for patients with progressive disease, uncertainty remains regarding the ecological validity of the results.

It therefore seems logical that in charting the way forward, efforts should be made to address each of these deficiencies. Focused interventions on well defined subgroups of patients (SPMS, PPMS, Expanded Disability Status Scale scores of 4–6 and >6) can provide answers fairly quickly. However, as our patients with SPMS constantly remind us, the clock is ticking, time is short, and the wheelchair waits. Therefore, further effort is needed—a bolder approach that combines more than one intervention with the aim of producing synergistic effects, with an improvement in one area boosting the putative benefits of therapy in another, so that the overall outcome exceeds the sum of the individual treatments. Such an approach often reflects the clinical reality of progressive multiple sclerosis in which several neurological difficulties rather than an isolated problem need to be addressed. To a limited degree, this approach has already been tried and the results are a source of cautious optimism.[106] What is now needed are similar initiatives, but on a much bigger scale, powered to ensure that final conclusions and recommendations are not undercut by sample size concerns. However, what might ultimately prove to be the most effective strategy could be a combination of multidisciplinary rehabilitative interventions plus new treatments directly addressing neurodegenerative processes such as oxidative stress and damage.[121] Studies like these will be complicated, costly, and logistically challenging. Yet these barriers need to be overcome. The Progressive Multiple Sclerosis Alliance, a coming together of multiple sclerosis societies from eight countries in association with the Multiple Sclerosis International Federation, endorses such an approach. In the absence of effective disease-modifying drugs, a combination of potentially synergistic treatments could offer the best opportunity yet to alleviate symptoms and improve function.

Contributors

AF participated in conceptualising the Series paper, completing the literature search, selecting articles for inclusion, writing the report, responding to reviewers' comments, and collating the contributions of the other two authors. JF and ACL were involved in conceptualising the article, completing the literature search, selecting articles for inclusion, writing the report, and responding to reviewers' comments.

Declaration of interests

AF has received grants from Biogen Idec and the MS Society of Canada; speakers' honoraria from Teva, Merck-Serono, and Novartis; and book royalties from Cambridge University Press, Johns Hopkins University Press, and Amadeus Press. ACL has received travel reimbursement from Hocoma and investigator-initiated grants from Acorda. ACL has also been on Acorda advisory panels related to multiple sclerosis. JF declares no competing interests.

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