Neurorehabilitation: applied neuroplasticity

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Neurorehabilitation in Multiple Sclerosis – Resilience in Practice

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In recent years, enormous strides have been made in increasing the range and efficacy of disease-modifying drugs available for the treatment of multiple sclerosis (MS) in its early and remitting stages, and more continue to emerge. Another equally important concept of successful treatment of MS is neurorehabilitation, which must be pursued alongside these medications. Key factors that contribute to the impact of neurorehabilitation include resilience and neuroplasticity. In the former, components such as nutrition, self-belief and physical activity provide a stronger response to the disease and improved responses to treatment. Neuroplasticity is the capacity of the brain to establish new neuronal networks after lesion damage has occurred and distant brain regions assume control of lost functions. In MS, it is vital that each patient is treated by a coordinated multidisciplinary team. This enables all aspects of the disease including problems with mobility, gait, bladder/bowel disturbances, fatigue and depression to be effectively treated. It is also important that the treating team adopts current best practice and provides internationally agreed standards of care. A further vital aspect of MS management is patient engagement, in which individuals are fully involved and are encouraged to strive and put effort into meeting treatment goals. In this approach, healthcare providers become motivators and patients need less intervention and consume fewer resources. Numerous interventions that promote neurorehabilitation are available, though evidence to support their use is limited by a lack of data from large randomised controlled trials. Combining interventions that promote neurorehabilitation with newer, more effective treatments creates a promising potential to substantially improve the outlook for patients at all stages of MS.

Keywords

Multiple sclerosis, resilience, neurorehabilitation, neuroplasticity

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Approaches to managing multiple sclerosis (MS) are changing rapidly and are achieving markedly improved efficacy in inhibiting the disease process.[1–3] As a result, treatment goals have progressed beyond halting disability progression. The most apparent reason for these achievements is the increasing use of disease-modifying drugs (DMDs) and the emergence of new DMDs that are more effective than those previously available. Despite these advances in DMDs and symptomatic therapies, there remains a need for comprehensive rehabilitation interventions in order to reduce disease symptoms, and to achieve maximal independence and quality of life, particularly in patients with progressive disease.[4]

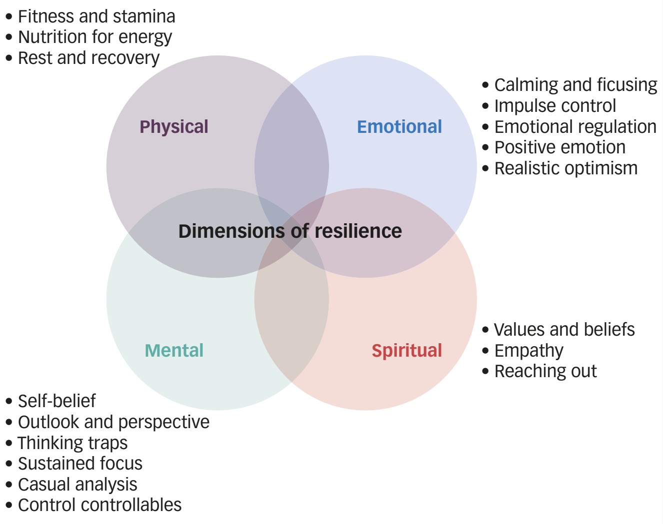
When initiating a neurorehabilitation programme, it is important to appreciate the value of maintaining resilience and neuroplasticity in MS patients and to understand the approaches that can encourage these factors and promote neurorehabilitation. Whilst DMDs can limit the occurrence of relapses and inhibit or delay disease progression, those developed so far have limited capacity to ameliorate all the existing disabilities that patients may have, particularly those with progressive disease. It is critical therefore that healthcare providers, who treat patients with MS, are aware of the potential of physical and cognitive therapies, and the benefits that neurorehabilitation can provide for the patient, especially when combined with DMD therapy. This review therefore considers the mechanism of action of neurorehabilitation in MS and interventions that can promote it in particular with respect to resilience and neuroplasticity.

Resilience in multiple sclerosis

In neurological conditions including MS, the concept of resilience is important in terms of impact of the disease and response to treatment. It is difficult to give a concise definition of resilience in the context of MS but it is related to psychological adaptation, social connection, life meaning, planning and physical wellness.[5] The concept of resilience comprises physical, mental and emotional components including good nutrition, rest and self-belief (see *Figure 1*). Without such activity and participation, there is insufficient neuronal stimulation, diminishing or eliminating the prospect of recovery. Patients must be encouraged to develop resilience in order to maximise their potential for regaining some degree of their lost physical abilities.

In a study of MS patients, the effect of occupational therapy on resilience was assessed.[6] The findings indicated that resilience has an important role in terms of functional recovery and maintenance. The authors concluded that the use of occupational therapy within multidisciplinary

Figure 1: Dimensions of resilience in response to disease and treatment



care has a crucial role and should be considered in the management of MS patients. Furthermore, Black et al. developed a holistic model of resilience, which was tested in people with MS.[7] Both direct and indirect pathways were identified to resilience and the findings suggest that psychological interventions to enhance personal resources and assets needed to cope would be effective in MS. These reports suggest that there should be a greater focus on resilience in managing MS patients.

The importance of neuroplasticity in multiple sclerosis

Neuroplasticity is another important concept in MS and is defined as the physical ability of the nervous system to adapt to changes. The recognition of recovery mechanisms in neurological tissue is not new; Constantin von Monakow proposed the idea of diaschisis, now known as neuroplasticity, in 1914.[8] This affects the ability of the brain to recover during neurological disease or after injury.[9] von Monakow believed that neurons in contact with or surrounding damaged brain areas, suddenly function abnormally or cease to function. This proposal was highly prescient and was confirmed by imaging and electrophysiological studies almost a century later.[10–12]

Neuroplasticity involves functional adaptations that occur at various different levels in MS.[13–17] At the cellular level, changes include axonal sprouting (increased arborisation of neurones), changes of synaptic stability and reorganisation of synapses. At the tissue level, there is resorption of oedema and rearrangement of Na-channels on axons beyond the nodes of Ranvier.[18] Re-myelination also occurs, even in adult brains. On the system level, takeover of functions occurs via the contralateral homologous cortex and enlargement of representation zones.

Results from a small cohort study (n=22) found that brain response to an electrical stimulus known as paired associative stimulation (PAS), a measure of neuroplasticity, may predict recovery from a relapse in RRMS.[19] Measures of neuroplasticity therefore potentially represent powerful markers that may enable physicians to determine optimal treatment for individuals with MS based on their ability to cope with brain tissue injury.

Not all of the changes in brain activity occurring in MS are adaptive, and thus behaviourally beneficial. Neuroplasticity can also be maladaptive and contribute to or sustain disability.[20,21] Furthermore, it is not known whether neuroplasticity is diminished with progressive disease. One study found that brain plasticity (measured as improvements with practice in performing visuomotor tasks) is preserved in MS patients with a high burden of cerebral pathology.[21] Another study showed that neuroplasticity in MS can be improved nearly to the same level as healthy controls when individuals are given repeated isometric visuomotor tracking tasks to perform.[9,20] With task practice, patients showed decreasing tracking errors and decreased areas of brain oxygenation, as shown by functional magnetic resonance imaging (fMRI). However, other investigations show that patients with primary progressive MS had impaired or absent brain neuroplasticity compared with those with relapsing-remitting MS (RRMS).[22]

At the behavioural level, neuroplasticity can be induced using novel motor and cognitive strategies, which counter problems of despair and resignation common to many MS patients. These principles were demonstrated in a study of rats given a single neurological lesion using pro-inflammatory cytokines.[23] Despite cellular damage and inflammation at the lesion site, function was restored over 28 days post-injury. At cortical sites remote from the lesion, reorganisation of neurones effectively bypassed the damage, suggesting high levels of neuroplasticity in animal brains. The authors of the study proposed that these findings provide a better understanding of endogenous repair capacity in the central nervous system and may help in the development of therapeutic strategies for this repair.

Further work on human brains using fMRI has shown that simple functions such as moving a hand involves more areas of the brain and more energy usage in non-disabled patients with MS than in normal control individuals.[24,25] Various other MRI studies in MS have indicated recruitment of related brain regions after damage has occurred at a specific lesion. These changes in brain connectivity affect various functions including motor function, cognition and memory.[26–29] In some conditions, such as stroke, there is restoration towards the original physiological network over time, whereas in MS this does not seem to occur and different and more complex patterns of network connections are established.[30–35] Studies have also shown that, following an initial increase in brain functional connectivity, it then declines over the following 2 years, resulting in a decreased ability to compensate for neuronal damage, which leads to disability progression in MS.[36]

These studies collectively provide evidence of functional change at brain sites remote from the injury or lesions in MS and stress the importance of treatments aimed at maintaining neuroplasticity and brain reserve to inhibit or prevent irreversible disability progression. In order to harness neuroplasticity to achieve neurorehabilitation, we need interventions that combine a strong scientific rationale and a strong biological rationale with monitoring of clinically meaningful functional and structural changes in the brain.[17]

Neuroplasticity is an important concept, both in terms of functional improvement and in directing future treatment. This was emphasised by the findings of a study that suggested platelet-derived growth factor (PDGF) plays a substantial role in promoting neuroplasticity in progressive MS.[37] Enhancing PDGF signalling might therefore be a valuable treatment approach.

Neuroplasticity is sustained by changes in the grey and white matter in the central nervous system, together with other tissues such as glial cells

Table 1: Symptomatic treatments used in multiple sclerosis

Symptoms	Drug interventions	Strategy/activities to address disability
Sensory disturbances	N/A	Active motor training Sensory stimulation Functional electrostimulation Constraint-induced training Tonus regulation Strength training/ aerobic training
Visual disturbances	N/A	N/A
Pareses	N/A	N/A
Gait disturbances	4-aminopyridine	Conventional, treadmill, Lokomat
Ataxia	Odansentron, isonicotinylhydrazine (isoniazid)	N/A
Spasticity	Antispastics intrathecal baclofen therapy, botox, tetrahydrocannabinol	N/A
Bladder disturbances	Antimuscarinics, botox, imipramine, solifenacin succinate, intermittent self-chatheterisation, pelvic floor physical therapy	N/A
Fatigue	Modanfinil*, amantadine*, carnitine*, pemoline*, alfacalcidol, vitamin D, 4-aminopyridine	N/A
Neurocognitive disturbances	Anticholinesterase inhibitors	Memory/attentional training Perception: neglect-training, visual compensation (Nova-Vision)
Eating/swallowing	N/A	Speech therapy
Speech	N/A	Speech therapy
Bowel and bladder function	N/A	Pelvic floor training
Depression	Antidepressants	N/A
Pain	Analgesics (e.g. NSAIDS, opiods, acetomenophen), tetrahydrocannabinol, anti-depressants (e.g., fluoxetine, citalopram and venlafaxine) and anti-seizure (off label e.g., gabapentin, pregabalin, clonazepam, carbamazepine, or amitriptyline), mindfulness	N/A

**Recent study findings suggest that modafinil, amantadine, carnitin or pemoline are not particularly effective in treating MS-related fatigue.[94] NSAIDS = non-steroidal anti-inflammatory drugs.*

and angiogenesis.[17] In order to develop novel interventions to promote or enhance plasticity underlying functional recovery, both experimental evidence and clinical studies are needed. In order to provide the best rehabilitation to people with MS, it is necessary to appreciate the interdependence between the body and nervous system and factors that contribute to motor sensory and cognitive functions.[38]

The need for neurorehabilitation in multiple sclerosis

MS has a complex symptomatology, which makes both diagnosis and treatment difficult. It is a diagnosis that is often arrived at after excluding other neurological conditions. In addition to an expanding range of more effective DMDs to address the underlying condition, various symptomatic therapies can treat other manifestations of the disease such as gait disturbances/mobility, ataxia, bladder/bowel disturbances, fatigue, depression and pain (see *Table 1*). Each person with MS requires a coordinated planning process that includes problem assessment, goal setting and identification of appropriate treatment regimens. Critically, there must be an education-training programme designed to enable or empower each patient with impairments to maintain (and regain) life activities.[39,40]

Neurorehabilitation strategies in multiple sclerosis

Strategies for neurorehabilitation in MS involve various different approaches. In addition to using appropriate and effective DMDs, it is critical to initiate therapeutic approaches including sensory-motor treatments (e.g. sensory stimulation and electrostimulation) gait (e.g. treadmill training) cognition (e.g. memory and attention training) speech therapy, and eating and swallowing therapy (see *Table 2*).[41–49]

Patient engagement

A key requirement for achieving neurorehabilitation in MS is patient engagement; without some degree of effort and belief from the patient, neurorehabilitation interventions in MS are less likely to succeed. Patient engagement can be encouraged through several actions including: setting and facilitating engagement by education and confidence-building and increasing the importance placed on quality of life (QoL) and patient concerns through patient-reported outcomes (PROs).[50] Patient engagement has been described as "the blockbuster drug of the century" due to its positive effects in treating various chronic diseases.[51]

In 2011, the MS in the 21st Century Steering Group was established, with the aim of improving outcomes in MS.[52] A key theme identified within the group's aims was the need for patient engagement. This factor can also be promoted by providing credible sources of accurate information, encouraging treatment adherence and empowering through a sense of responsibility. When patients are engaged, they are more likely to consume fewer healthcare resources, and to report issues and adverse events with treatment. As a result, such patients have an important role in improving the quality, safety and cost of interventions and in improving clinical outcomes.[51,53–56] One cross-sectional survey of MS patients ($n=199$) found that MS-related QoL and MS-related self-efficacy correlated significantly with patient activation in MS patients ($r=0.42$, $p<0.01$ and $r=0.50$, $p<0.01$, respectively). Conversely, depression had an inverse correlation ($r=-0.43$; $p<0.01$).[57]

Physical activity

Physical activity is an important component of neurorehabilitation and has been shown to confer numerous advantages in MS.[58–64] Physical

Table 2: Therapeutic strategies to address various disabilities resulting from multiple sclerosis

Disability/symptom type	Strategy/activities to address disability
Sensory-motor	Active motor training Sensory stimulation Functional electrostimulation Constraint-induced training Tonus regulation Strength training/aerobic training
Gait	Conventional Treadmill Lokomat
Cognition	Memory/attentional training Perception: neglect-training Visual compensation (Nova-Vision)
Speech	Speech therapy
Eating/swallowing	Speech therapy Swallowing assessment and therapy
Bladder and bowel function	Pelvic floor training
Activities of daily living	Self-care Orientation training
Pain	Cryotherapy Soft tissue mobilisation Graded manual traction Muscular stabilisation exercises Neuromuscular facilitation Psychological techniques: hypnosis and virtual reality interventions
Other support	Technical aids Instruction of patients/caregivers Social service/reintegration

Source: Lo et al., 2008,[46] Renom et al., 2014,[48] Pepping et al., 2013,[47] Langdon, 2011,[45] DasGupta et al., 2003,[43] Buzaid et al., 2013,[42] Khan et al., 2015,[44] Svestkova et al., 2010,[49] National Clinical Guideline Centre, 2014.[41]

activity helps preserve good functional reserves that are needed to reduce the risk of relapsing function impairments.[65–67] Regular physical activity may exert its beneficial effects on MS through changes in neuroactive proteins such as upregulation of insulin-like growth factor-I, which appears to act as a neuroprotective agent, as well as neurotrophins, brain-derived neurotrophic factor (BDNF) and nerve growth factor.[68] Exercise has also been found to moderate brain volume changes in patients with Alzheimer's disease,[69] and restore some of the losses in brain volume associated with normal aging.[21,69] In a 2007 study, 24 patients with RRMS underwent a fitness assessment and were scanned in a 3-tesla MRI system during the Paced Visual Serial Addition Test (PVSAT).[70] Higher fitness levels were associated with faster behavioural performance and greater recruitment of right inferior frontal gyrus/ middle frontal gyrus (IFG/MFG), a region of the cerebral cortex recruited by MS patients during performance of PVSAT to compensate for the cognitive decline caused by MS. A further study found that higher levels of fitness were associated with greater grey matter volume in the midline cortical structures including the medial frontal gyrus, anterior cingulate cortex and the precuneus. The authors concluded that fitness has a prophylactic effect on the cerebral atrophy observed early in the disease process, and may reduce long-term disability.[71] However, these were small, cross-sectional studies and larger trials are required before meaningful conclusions may be drawn.

In a systematic review and meta-analysis of 12 controlled clinical trials investigating the effects of exercise intervention programmes on cognition in people with MS, stroke or Parkinson's disease, significant improvements in cognition were found in nine of the 12 studies.[72] However, the total effect size was non-significant for changes in executive functions, due to inconsistencies between measures of cognition, training sequences and intervention period. A neurorehabilitation technique termed constraint-induced movement therapy involves intensively training use of a patient's arm that is affected by MS while constraining movements of the other, less-affected, arm using a sling for 90% of waking hours for 2 weeks.[73] This approach has proven beneficial in progressive MS: in a preliminary study, patients (n=5) showed significantly improved limb use at post-treatment and 4 weeks post-treatment, along with improved fatigue ratings and maximal movement ability as assessed in a laboratory motor test. Data from stroke patients suggest that this therapy induces neuroplastic changes in the structure and function of the CNS.[74] Other interventions include electromyogram-triggered neuromuscular stimulation, and robotic interactive therapies, but these have not been studied extensively in MS patients.[59]

Gait

In addition to simple physical exercise, gait training is also an important aspect of improving walking and mobility in MS. One study on 35 patients with MS showed that patients who used a robot-assisted treadmill to guide their walking gait experienced greater improvements in walking abilities compared with those who received conventional walking therapy.[75] This gait training reduces physical load during walking, provides an efficient training of leg muscles and postural stability and enhances central adaptive processes. Parameters of walking (effect sizes) were not significantly improved versus convention walking but there were improvements in walking velocity, walking distances and knee extensor strength. This is a feasible type of gait training in MS but is likely to be of greater value to patients with severe walking disabilities.

Cognitive neurorehabilitation

Various cognitive neurorehabilitation strategies have been proposed in MS. A small study (n=15) found that a cognitive rehabilitation programme increased brain activity in the cerebellum of cognitively impaired patients with MS.[76] In a double-blind, randomised controlled trial, computer-assisted cognitive rehabilitation of attention deficits increased fMRI activity in the posterior cerebellum and in the superior parietal lobule of 12 patients with MS compared with 11 matched MS patients receiving a placebo intervention.[37] However, a Cochrane review concluded that heterogeneity of studies limits the strength of the evidence in favour of cognitive rehabilitation in MS.[77]

Body temperature

In 1890, ophthalmologist Willhelm Uhthoff observed that increased body temperatures, arising from physical exertion, resulted in transient impairment of vision in patients with MS.[78] Later work showed that in nerve fibres of the central nervous system (CNS) with increasing loss of myelin and decreasing conduction velocity, there is conduction block at progressively lower temperatures.[79] This observation led to the contention that reducing body temperature in MS patients during exercise could increase central motor conduction and reduce disability. Electrophysiological studies on a group of 20 patients who were immersed in cold water showed increased motor conduction, demonstrating that Uhthoff's phenomenon was valid in MS.[80] The findings indicated that MS patients are more vulnerable to nerve block due to increased temperature than normal individuals. More recently, cooled wearable pads and garments have been successfully used as a method of combating increased heating in MS patients during exercise and maintaining motor function.[81]

Pain

Treating pain is an essential strategy in neurorehabilitation in MS. Recently, the Italian Consensus Conference on Pain in Neurorehabilitation published two articles evaluating the role of pharmacological and non-pharmacological strategies in the treatment of pain in neurorehabilitation. In the first, cryotherapy, soft tissue mobilisation, graded manual traction, exercises for regaining range of motion, deep flexors stabilisation exercises and proprioceptive neuromuscular facilitation were identified as useful in the treatment of cervical pain in MS.[82] In the second, the investigators performed a systematic review of 400 studies evaluating the effect of psychotherapies on pain intensity in neurological disorders.[83] For chronic pain associated with multiple sclerosis, hypnosis and virtual reality interventions were recommended. The authors concluded that psychological interventions are safe and effective treatments that can be used within an integrated approach for patients undergoing neurological rehabilitation for pain.

Assessment of neurorehabilitation strategies

Neurorehabilitation is a critical part of treatment in MS but evaluating its effects is problematic. In neurorehabilitation there is a lack of standardisation of methods making comparisons between studies difficult. There is also a reluctance to use a control group, difficulties with blinding and a lack of consensus on outcome assessments for determining parameters such as impairment, disability, quality of life, goal achievement, coping skills and self-efficacy. There is also a variable choice of goals that are clinically useful, scientifically valid and appropriate to the population studied.[84,85]

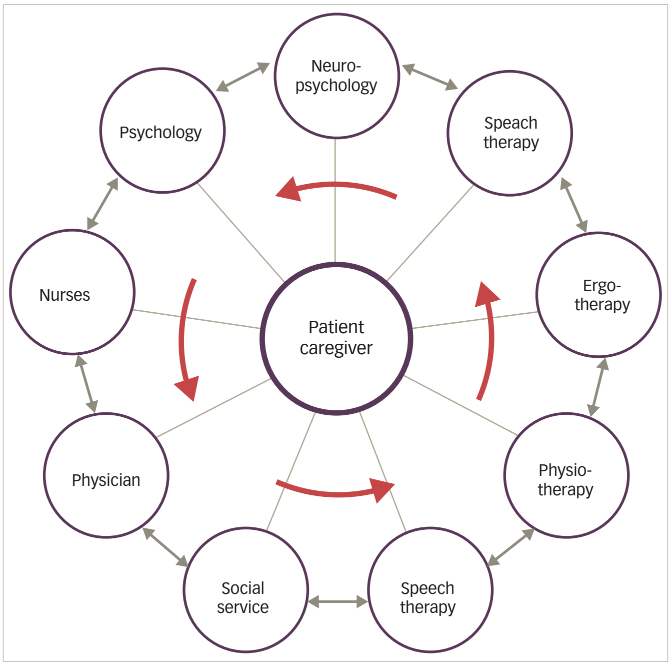
Multidisciplinary approaches

To adopt the above strategies and rehabilitate a person with MS requires a multidisciplinary team that centres on the patient and their caregiver, and takes into account the individual's history.[86–90] This team should involve a neurologist trained in rehabilitation medicine, and multiple other therapists including speech therapists, psychologists, MS nurses, orthopaedic technicians, physiotherapists, ergotherapists and social service representatives (see *Figure 2*). All should interact and operate in a coordinated way and work to an integrated clinical care pathway. This should include patient-defined needs and goals, and therapists' assessment of problems (mobility, self-care ADL, communication, daily occupations and social interactions). Setting of common goals should be performed at an interdisciplinary level and should be clear, specific, meaningful, realistic and measurable (e.g. "In seven days you will be able to climb stairs or dress yourself"). Assessment of goal achievements should be regular and goals adapted if necessary. A Cochrane review identified eight trials (seven randomised, 747 participants and 73 caregivers) investigating multidisciplinary rehabilitation programs in MS.[91] Although limited, available evidence suggested that inpatient or outpatient rehabilitation programmes may improve disability, bladder dysfunction, and participation, and the effects may last up to 12 months.

Conclusion

Significant advances have been made in effective DMDs in recent years and their availability has substantially improved the prognosis for patients with clinically isolated syndrome or RRMS. The outlook for patients with more progressive disease, however, is less optimistic.[92] Nevertheless, at most stages of MS there remains a great need for personalised regimens that aim to maximise resilience and neuroplasticity by stimulating the individual to strive for improvement and actively participate in their neurorehabilitation process. The human brain has sophisticated mechanisms for recovery of function

Figure 2: Coordinated interaction between specialities that is needed in the neurorehabilitation of a patient with multiple sclerosis



at sites distant from an MS lesion that compensate for damage. This altered neuronal function has been clearly demonstrated in fMRI studies on MS patients. Stimulating such mechanisms, however, requires effort from the patient and encouragement/guidance from healthcare providers. Successful neurorehabilitation requires a multidisciplinary team that centres on the patient and their caregiver who all work to a defined clinical care pathway with clear achievable goals for which progress is frequently monitored. Providing such intensive individual attention to all patients with MS is a challenge since access to treatments and services in MS across Europe is highly variable and often limited by the availability of healthcare resources.[93]

Neurorehabilitation takes many forms depending on the various physical or mental manifestations of the disease in each patient and the problems they encounter. Some of these symptoms can be addressed using an increased range of drug therapies such as 4-aminopyridine to improve mobility in patients who respond, antimuscarinics for bladder control and modanfinil for fatigue. Other symptoms, however, require treatments that harness the neuroplasticity of the CNS, i.e., its innate ability to adapt to change. These include physical therapy such as exercise programs and gait training whereas others require cognitive or psychiatric therapy. Numerous studies have demonstrated the considerable value of such interventions and these are especially effective when used in conjunction with DMDs. MS treatment should be holistic and address all of the patient's symptoms and concerns; it is vital that a multidisciplinary approach is taken rather than relying on DMDs alone. It is essential, however, the standardised measures and endpoints for determining neurorehabilitation interventions are agreed in order to properly assess their value in different MS patient populations around the world.

There are now strong grounds for optimism in MS management. Increased use of newer medications coupled with defined programmes of education/training and goal setting are likely to substantially improve the prognosis in many patients, particularly during the early disease stages. These interventions collectively promote neuroplasticity and neurorehabilitation and have the potential to halt further neurodegeneration. As a result, patients diagnosed with MS today can expect substantially more active lives, generally better outcomes and possibly some recovery of lost function.❑

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